

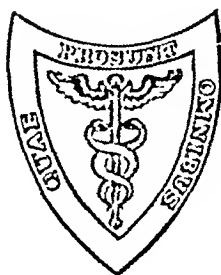
THE
AMERICAN JOURNAL
OF THE
MEDICAL SCIENCES

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NEW SERIES

VOL. 196



LEA & FEBIGER
PHILADELPHIA
1938

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THE
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OF THE MEDICAL SCIENCES

JULY, 1938

ORIGINAL ARTICLES.

THE EVOLUTION OF THE PARENCHYMAL LUNG LESIONS IN
RHEUMATIC FEVER AND THEIR RELATIONSHIP TO
MITRAL STENOSIS AND PASSIVE CONGESTION.

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CARDIAC involvement is the main object of interest in rheumatic fever to both the clinician and pathologist. There is often, however, a pulmonary change in that disease that is in many respects equally important and indeed responsible for some of the signs and symptoms that have been attributed to the heart itself.

This report deals with the evolution of the pulmonary lesions of rheumatic fever, tracing the relationship of the acute pneumonia or pneumonitis to the chronic pathologic changes seen in the lungs of patients who have mitral stenosis and other evidences of advanced rheumatic heart disease. This study was undertaken in connection with the larger problem of the possible influence that such pulmonary changes might have on the evolution of rheumatic heart disease. We do not believe that the pulmonary changes in late rheumatic heart disease are to be ascribed wholly to congestive failure. Contrariwise, we are led to believe that these can be attributed in major part to recurring inflammation, such as may be seen in the heart in the prolonged course of rheumatic disease.

The pulmonary lesions of rheumatic fever are: 1, the parenchymal; 2, the vascular; 3, the pleural. We deem the first two important in the development of the chronic cardiopulmonary state of rheumatic disease. Pleuritis is a common feature but probably

has little influence on the course of cardiac disability, except in those uncommon instances where adhesion is complete and bilateral.¹² It is therefore only briefly mentioned and the reader is referred to Paul's¹⁰ work for detailed discussion. The lesions should be further divided into: 1, acute; 2, subacute; 3, chronic.

The Acute Phase of Rheumatic Pneumonopathy. The clinical aspects of the pneumonia and pneumonitis^{5a} will not be repeated in this report, but the pathologic changes will be reviewed and certain features discussed in detail because of their importance as connecting links in the transition from the acute inflammatory to the late chronic stages of the pneumonopathy. This acute lung lesion is an interstitial hematogenous inflammation having the same pathogenesis as carditis and arthritis. It varies greatly in severity and extent, appearing in some instances as small isolated foci of hemorrhagic pneumonitis and in others as a widespread pneumonic consolidation. The lower lobes are usually more extensively involved but the upper lobes may be equally affected; the process is generally bilateral and commonly extends in a "wandering" transient manner.

Congestion and hemorrhage are often striking features contributing not only to the consolidation proper but giving it a richly varied color—dark red, occasionally a deep purplish-blue, contrasting with the pallor of adjoining uninvolved areas or the rusty-brown of subsiding congestion. Numerous small hemorrhagic foci are often scattered over the non-consolidated areas and have the same essential relationship to the rheumatic process as the major lesions of pneumonitis and consolidation. Although an entire lower lobe may be involved, consolidation is usually not so bulky as that of pneumococcic pneumonia; more often it is incomplete, excised sections showing a variable tendency to sink in water or to do so slowly. Section reveals a deep red or reddish-brown parenchyma with a smooth almost non-granular surface and liver-like consistency. In the past, this consolidation has been most often regarded as an atelectasis; the latter often does develop as a later complication. Rheumatic pneumonitis is essentially a non-suppurative lesion. The bronchial mucosa is congested but generally free of purulent exudate; empyema or abscess are rarely seen, then only because of secondary infection.⁵

There are variations from the typical picture that are worthy of brief comment. In some cases of fulminating rheumatic fever, pulmonary congestion with hemorrhage are so marked as to obscure the inflammatory features of the lesion. Striking examples in children were described by Coburn.² Lesser grades of congestion are commonly noted and often regarded merely as acute passive hyperemia, incidental to heart failure. The hemorrhagic factor occasionally leads to an atypical infarction, a dark red, poorly demarcated consolidation, not having the classical wedge or triangle

shape, the dry appearance or necessarily the subpleural localization of the ordinary infarct. It may pass for rheumatic pneumonia (of which it is usually a part) and is identified usually by histologic examination which further reveals its atypical nature.

The Histopathologic Change in Acute Rheumatic Pneumonopathy. The acute interstitial inflammation in the rheumatic lung is seen as a thickening of the alveolar walls through capillary congestion, edema, focal necrosis and cellular infiltration. The capillary congestion is often intense and accompanied not only by edema of the septa but by escape of fibrin to the alveolar spaces causing further consolidation of the tissue. The inflammatory reaction may be conveniently divided into three stages: 1, destructive; 2, proliferative; and 3, reparative.

The initial destructive phase is characterized by foci of fibrinoid necrosis in the alveolar walls with cellular infiltration of monocyte variety, apparently of reticular and endothelial capillary origin.* These cells, deeply stained, are of various shapes, often fragmented and usually associated with sparse numbers of similarly fragmented neutrophils (Figs. 1 and 2). The fibrinoid necrosis while usually focal is occasionally widespread, involving the entire wall of an alveolus or of contiguous alveoli, with marked destruction of the elastic and reticular framework. In severe cases of rheumatic pneumonia the alveolar walls may be converted literally into "ribbons" of fibrin (Fig. 3). The congested capillaries often undergo a hyaline thrombosis and lose their integrity. Cellular infiltration into the alveoli is usually scant, consisting of phagocytes, desquamated alveolar cells and occasional neutrophils. Dense infiltration of the latter is uncommon.

The second or proliferative phase is marked by the infiltration of larger basophilic cells, often with vesicular nuclei, sometimes multinucleated; they are the so-called "Aschoff" cells, often in perivascular groups, spreading out into the interstitial tissues, not subject to the necrosis and fragmentation described above and apparently replacing the initial cellular invasion.

The third stage, which we assume to be a reparative reaction, consists in the presence of infiltrated plasma cells and lymphocytes, and proliferated fibroblasts. Elaboration of collagenous material by fibroblasts becomes more and more evident. These changes often coexist in the same section blending into each other with little or no demarcation. At times the intermediate or proliferative reaction is apparently slight, the reparative process following quickly on the initial destruction.

The Aschoff nodule common to the myocardium is seldom encountered in the lung; however, the fundamental morphologic changes

* The term "epithelioid" formerly applied to this monocyte infiltration has been discarded; its use had been suggested by the resemblance of the early monocytes to those of tubercle and other granulomas; they probably have a similar origin.

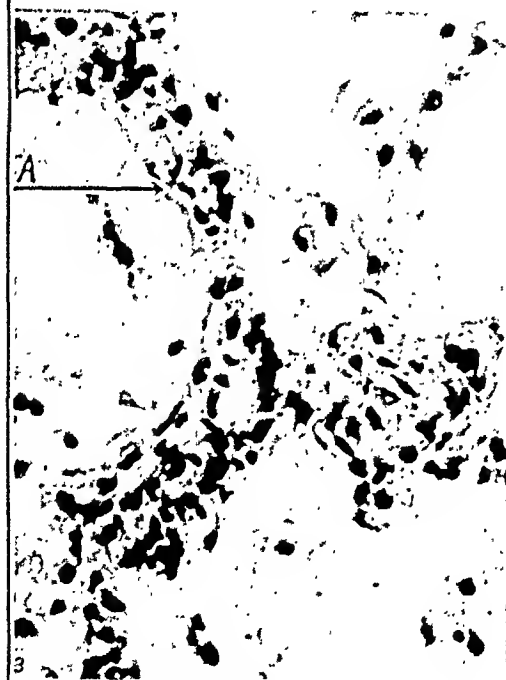
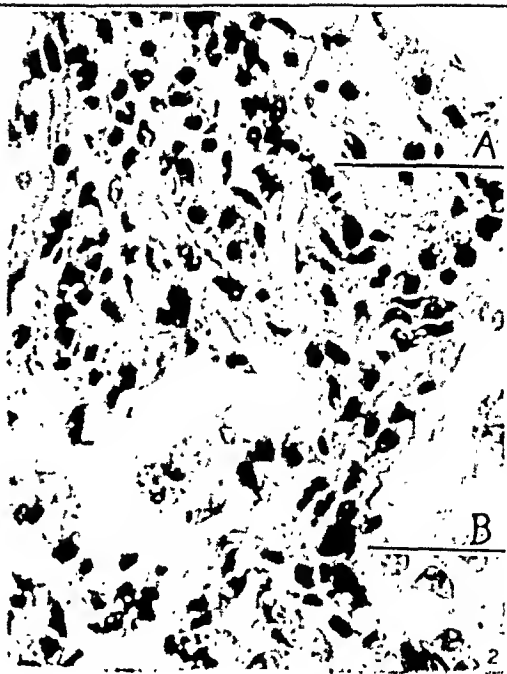
inherent in the formation and "life cycle" of the classical nodule are all seen in the interstitial pneumonia of rheumatic fever, namely, the initial focal fibrinous (fibrinoid) necrosis, the later proliferative infiltration of macrophages, the final fibrosis. The interstitial structure of the lung possibly does not lend itself readily to the formation of nodules. It is not uncommon, however, to find seminodular perivascular aggregations of macrophages, and in some cases characteristic Aschoff bodies were noted, not merely in the subpleural tissue⁴ but in the lung parenchyma.⁶ An exhaustive search through a number of sections would probably reveal their presence in greater number than heretofore described.

Variations in the histologic picture correspond to those noted in in the gross. Often the marked congestion obscures the other inflammatory aspects, but it differs from the purely passive hyperemic state in that it is accompanied by marked hyperplasia of the capillary endothelial and interstitial reticular cells and their migration in large numbers into the tissue spaces. In many instances, marked congestion, the presence of so-called "Herzfehler Zellen" and undue reticulo-endothelial cellularity are at first glance the only changes noted in the acute rheumatic lung lesion. Continued search, however, will usually show foci of early fibrinoid necrosis, with cell fragmentation.

"Inflammatory Infarction" in Rheumatic Pneumonia. In ordinary infarction, a mere skeletal framework of the alveolar structure remains unaccompanied by any viable cell structure. We have noted infarction on 6 occasions in rheumatic pneumonopathy where the interstitial tissue was tremendously thickened by fibrin and cellular exudate, the new cells maintaining some degree of viability. Obliterating rheumatic arteritis is usually a part of this lesion.

The Destruction of the Elastic and Reticular Network. The destruction of the normal elastica, probably common to many types of pneumonia, seems of greatest significance in the rheumatic pneumonopathy where the inflammation is primarily interstitial and featured often by necrosis. The normally delicate elastic fibers are broken and disintegrated, appearing in the Weigert stained preparation as fragmented threads or as irregular dots, in many places being quite lost (Fig. 4). This is apparently the basis of the subsequently impaired elasticity of the lung tissue following rheumatic pneumonitis.

The Subacute Phase of Rheumatic Pneumonitis. The subacute phase is a continuation of the reparative process just described. It is featured by: 1, Marked changes in the consistency of the involved lung tissue; and 2, basal atelectasis (inconstant). The subacutely inflamed lung, although not consolidated, remains poorly aerated and often should a whole lobe or a large part of one be involved, is somewhat smaller than normal. The color varies from dark red to reddish (rusty) brown and the subpleural lymphatics



A

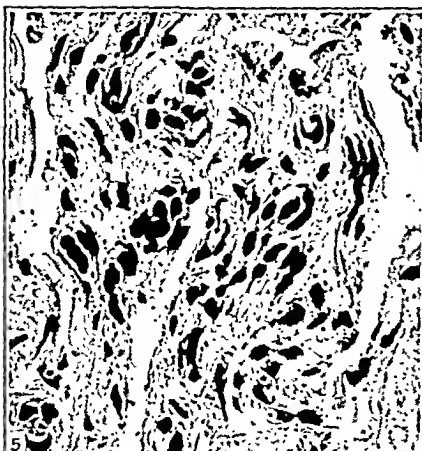
B

FIG. 1.—Acute rheumatic pneumonitis; dense focal infiltration of monocytes, including large multinucleated Aschoff cells (A) in a focus of "fibrinoid" necrosis, with obliteration of the alveolar structure ($\times 552$).

FIG. 2.—Acute rheumatic pneumonitis; fibrinous swelling and necrosis of alveolar wall with seminodular infiltration of monocytes of varied shape and size, some of them fragmented (A). An occasional polymorphonuclear and lymphocyte are seen; also larger deeply stained multinucleated cells (B) ($\times 460$).

FIG. 3.—"Fibrinoid" necrosis of alveolar walls in acute interstitial rheumatic pneumonitis (A) ($\times 308$).

FIG. 4.—Destruction of interalveolar elastica in acute rheumatic pneumonitis. Small shreds and dots of elastica remain; it is better preserved in the small blood-vessels (V).



FIGS. 5, 6, 7, 8, 9 and 10.

are often prominent as a gray web. The pleural surface may show localized plastic pleurisy, and easily broken fresh adhesions are often seen laterally and especially in the interlobar fissures. Small to moderate-sized pleural effusions with increased fibrin content are commonly observed, while hydrothorax of true congestive failure is less often encountered. Section reveals tough lung tissue having a rubberoid consistency, cutting with an increased resistance, the cut edge remaining rather sharp. The cut surface may be moderately moist or in some cases quite dry. Inspection of the pulmonary artery and its larger branches usually reveals nothing of note in young subjects in whom rheumatic involvement has been recent. The striking change from the normal lung lies in the altered elasticity.

Microscopic examination reveals early diffuse interstitial fibrosis, replacing the monocyte-macrophage infiltration (Fig. 5). Often the transition is uneven, there being foci of acute pneumonitis in close proximity to early fibroblastic activity. We wish to emphasize that this fibroblastic process is in direct sequence to an acute inflammatory reaction and not to passive congestion. Marked pulmonary edema is not often noted in these microsections, and usually the congestion associated with acute pneumonitis has already subsided although a certain amount of interstitial edema persists. In many instances, there are numerous "Herzfelder" phagocytes both within the interstitial tissue and in the alveoli. In this sub-acute phase there is noted the early regeneration of the elastic tissue; the peculiar aspect and probable significance of this regeneration will be commented upon later.

Necropsy in the subsiding phase of rheumatic fever (corresponding with the subacute and subchronic phases of rheumatic carditis and pneumonitis) often reveals characteristic basal collapse or atelectasis, which usually but not necessarily is associated with pleural effusion. The degree of pulmonary collapse occurring with rheu-

LEGENDS FOR FIGS. 5, 6, 7, 8, 9 AND 10.

FIG. 5. —Subacute phase of rheumatic pneumonitis. Note fibrocytosis and deposition of collagen. There is collapse of alveoli (lobular atelectasis) ($\times 460$).

FIG. 6. —Marked thickening of alveolar wall by collagen in subchronic rheumatic pneumonitis. Note small foci of recurring inflammation (A) ($\times 184$).

FIG. 7. —Low-power view of late chronic post-rheumatic interstitial pneumonitis. There is marked pulmonary impairment, with irregular fibrotic thickening of the alveolar walls (X). An occasional focus of emphysema is noted. A larger muscular branch of the pulmonary artery is normal, while two arterioles (A) are slightly to moderately thickened ($\times 80$).

FIG. 8. —Recurring acute rheumatic pneumonitis in late chronic phase of the lesion.

FIG. 9. —Hyperplasia of intervalveolar elastica ("pulmonary elastosis") of chronic rheumatic pneumonitis from a patient, aged 37, with mitral stenosis, pulmonary hypertension and cor pulmonale. Death by right heart failure. Note coarse deeply stained and disrupted elastica; Weigert stain ($\times 230$).

FIG. 10. —Control section from normal lung of woman, aged 28; note delicate elastica and normal alveolar structure; Weigert stain ($\times 276$).

matic pneumonitis is sometimes very striking. For many years it has been ascribed to pleural and more often pericardial effusion and localized to the left base. Both Naish⁸ and ourselves^{5a} have noted that basal collapse can occur as well on the right side. The pleural effusions so commonly seen are mostly of inflammatory origin, and, although coëxisting rheumatic myocarditis is almost inevitable, congestive heart failure is a major factor in only a minority of these patients. We believe that impaired elasticity of the lung is the basis for this atelectasis, and that such altered lung tissue is exceptionally vulnerable to pressure, whether exerted by accumulation of pleural or pericardial fluid or by elevation of a temporarily inactive left diaphragm.³

Chronic Stage of Rheumatic Pneumonopathy. Patients dying with chronic rheumatic heart disease, with or without advanced mitral stenosis, show in the large majority a pathologic change in the lung structure. Hitherto the attention of the pathologist has been directed to the presence of hydrothorax, pulmonary edema, infarction and, in view of the recent knowledge of pulmonary arterial hypertension, to the state of the pulmonary arteries which often exhibit considerable atherosclerosis. The lungs will commonly show a denser consistency, and usually remain semi-inflated on removing the chest plate. They may be grayish or else reddened in varying degree by congestion. Old pleural adhesions, basal or lateral, are commonly noted and occasionally the entire lung is covered by thickened opaque pleura. Section will reveal a rather firm inelastic structure in which, with the aid of a hand lens, the alveoli can be seen standing out as a well-supported, somewhat stiffened honeycomb that resists the deflating effect of atmospheric pressure, the result of interstitial fibrosis. In many cases the altered consistency is readily apparent and amounts to a diffuse toughness. In discussing the subacute pulmonary lesion we used the term "rubberoid," which may well be applied to the chronic state. Such lungs are cut with more precision than the normal because of the increased resistance. A certain amount of emphysema is not uncommon to the lungs of the chronic rheumatic state. This is a secondary effect, however, following the interstitial fibrosis and the loss of the normal elastica and is best seen in marginal sites, anteriorly and at the bases; occasionally it is of the advanced "bullous" variety. This increased resistance, the impaired deflation and the secondary emphysema are not limited to the lower lobes, but can be noted as well in the upper lobes, usually however in lesser degree. The fibrosis is sometimes associated with moderate anthracosis, in which event the lung tissue is considerably tougher than is ordinarily seen with the latter condition alone. It may be accompanied by focal induration, usually in the lower lobes and possibly the result of healed infarction or the sequel of previous basal collapse.

The Histopathologic Picture of Chronic Post-rheumatic Pneumonitis. Histologic examination of the gray semirigid or "rubberoid" lung will show the alveolar walls thickened with collagenous fibrosis, the extent of which may vary greatly even from field to field in the same section, perhaps involving large areas uniformly. More often a portion of an alveolar septum will be replaced by fibrous tissue yielding in the aggregate a patchy involvement rather than a diffuse and complete interstitial fibrosis. The thickness of the affected alveolar wall is at times extreme, as much as 60 microns. The process was termed pericapillary fibrosis by Moschcowitz⁷ and its development around the pericapillary basement membrane rather than along the outer subalveolar membrane was beautifully illustrated by Parker and Weiss.⁹ It is often associated with some degree of pericapillary edema which is probably due to compression and localized obliteration of lymphatic and blood capillary network. With marked fibrotic thickening and diminished capillary blood supply there is frequently an associated metaplasia in the alveolar lining cells, the latter becoming cuboidal. This fibrosis following rheumatic pneumonitis is not the same as the carnification or delayed resolution of ordinary pneumonia, in that the process is interstitial and the alveolar spaces are preserved even though focal atelectasis does occur. Small foci of recurring acute pneumonitis are not uncommonly seen in the toughened lungs of patients who have had chronic rheumatic disease of long standing (Fig. 8).

Differential stains (Weigert) show in many instances a marked hyperplasia of elastic tissue in the form of thick, coarse, deeply stained fibers, often irregularly banded, often disrupted and fragmented (Fig. 9). They are most prominent in those alveolar walls that are thickened by collagen fibrosis and appear to be a considerable part of that fibroblastic reaction. This hyperplasia possibly starts as a regenerative process following acute rheumatic pneumonitis in which the normal elastica is largely destroyed; at least, in subchronic phases of the rheumatic pneumonopathy the beginning of the hyperplasia is often noted. The new elastica can apparently be destroyed as was the preceding normal structure by recurring acute interstitial pneumonia. The hyperplasia may develop to a remarkable degree. We have used the term "elastosis" in reference to its histologic picture. It is apparent that this abnormal elastic tissue does not have the functional value of the delicate elastica of normal lung parenchyma. The elastic recoil is lost; there is noted instead on palpation an increased resistance almost reminiscent in some cases of India rubber. A similar hyperplasia of elastica is to be noted in other previously elastic structures that have been subjected to increased strain, *e. g.*, the diseased heart valves of rheumatic and syphilitic heart disease and in the intimal coats of arteries. Pulmonary elastosis is really a common finding in patients with chronic rheumatic heart disease occurring in connection with pul-

monary interstitial fibrosis and at the same time with pulmonary hypertension and hypertrophy of the right ventricle. We have been impressed with the apparent parallelism of these findings in many cases. Pulmonary elastosis is not pathognomonic of the chronic rheumatic pneumonopathy, however, since it is found to some degree with advanced pulmonary interstitial fibrosis regardless of the underlying pathologic change. Its development, therefore, has a mechanical rather than a purely etiologic significance. It is of interest, however, that a moderate degree of elastic tissue hyperplasia is already evident in the lung sections of a majority of young rheumatic fever patients. In these patients the mitral valvular lesion is comparatively slight, certainly not that of stenosis, a fact that suggests to us that the obstructive process that causes right heart strain begins early within the lung structure in rheumatic fever.

The toughening of the lung has always been attributed to pulmonary passive congestion. However, it is often demonstrable in young rheumatic patients who never had definite congestive heart failure, except possibly in the last few days of life. The "rubbcroid" lung in rheumatic heart disease in the subchronic and chronic state is usually distinctive in its consistency from that of the lung in chronic congestive heart failure, *e. g.*, after myocardial infarction or other lesions leading to chronic left ventricular failure with recurring pulmonary edema. In the latter case, the lung is often merely boggy from passive congestion. Since low-grade pneumonitis of varied bacterial origin is apt to develop in the presence of passive congestion,¹ it is not surprising to encounter occasionally increased firmness of the lung where congestive heart failure irrespective of etiology is the fundamental factor. The chronic pulmonary congestion of syphilitic heart disease is not infrequently accompanied by a mild fibrosis which, however, may be partly of infectious origin. The surprising thing is that interstitial fibrosis incidental to heart failure *per se* is often so slight in the non-rheumatic cases. On the other hand, a varying degree of toughness is found in the large majority of cases of chronic rheumatic heart disease regardless of the extent of congestion, often irrespective of the severity of the associated valvular heart lesion. Incidentally, we have noted its absence or slight development in a smaller group of patients with even advanced mitral stenosis, a fact that indicates to us that valvular disease *per se* is not the main causative factor of pulmonary interstitial fibrosis.⁵

Passive Congestion and the "Dry Lungs" of Chronic Rheumatic Heart Disease. Pulmonary congestion in chronic rheumatic heart disease depends on many factors. Some of these gray toughened lungs are strikingly free of passive congestion, while many, of course, show it in marked degree with or without pulmonary edema due to

heart failure. Not uncommonly, late pulmonary congestion is the result of a combination of factors: a recurrence of rheumatic activity as indicated by the presence of pneumonitis and carditis and associated terminal heart failure. This is often seen in the final cardiac defeat of middle-aged rheumatic patients, who die shortly after a mild respiratory infection, usually beginning in the upper respiratory tract. The altered consistency of the lung parenchyma due to previous attacks of pneumonitis is usually easily demonstrable despite the terminal congestion.

Severe chronic passive congestion with paroxysmal pulmonary edema is not as common in rheumatic heart disease as in other types of cardiac disease. While terminal congestion and edema are usually present, the lungs at necropsy are often comparatively dry. In many instances small foci of acute congestion with moderate escape of edematous fluid are separated by wide areas of non-congested lung tissue. There is in our experience a small but definite number of cases where the lung structure was rather strikingly dry, although there may have been coëxisting hydrothorax, and congestive failure in the remaining viscera. There may be curiously enough a greater degree of hyperemia in the bronchial mucosa, due possibly to marked congestion in the bronchial veins and capillaries. It is commonly thought that, even in the absence of decompensation, the lungs are the site of constant passive hyperemia due to back pressure secondary to mitral stenosis. For example, this was the reason advanced by Peabody for the decreased vital capacity noted in individuals with compensated valvular heart disease.¹¹ We are convinced that this is not necessarily so; in the occasional case of more or less sudden death in patients known to have compensated mitral stenosis we have seen no evidence of this supposed blood stasis. It is even more puzzling to observe such findings where heart failure with congestion of the viscera has actually occurred. Tri-enspid stenosis and obstruction of the inferior vena cava, factors known to cause a relative ischemia of the lungs, were not factors in our material. These dry lungs for which we have no adequate explanation were mentioned casually by Paul,¹⁰ but, as far as we know, no other reference to them exists in the literature.

The Relationship of Pulmonary Arterial Lesions to Rheumatic Pneumonopathy. In this paper we have not attempted to discuss the vascular lesions of rheumatic pneumonopathy. It is well known that in late rheumatic heart disease with mitral stenosis, advanced arteriosclerosis of the pulmonary artery may be present, involving especially the smaller branches. The extent of this development varies and does not appear to be in constant relationship to the parenchymal damage (Fig. 7). Unquestionably such extreme involvement as is sometimes seen must play an important rôle in the development of right heart strain. It may possibly introduce the

factor of ischemia in the development of chronic pneumonitis. This arteriosclerosis has its origin in part in rheumatic arteritis. We have observed the early appearance of pulmonary arteritis in acute rheumatic fever; it is generally collateral with the parenchymal changes and in a few instances by reason of extensive and unusually severe involvement, is the predominant lung lesion. However, it is our opinion that arteritis and arteriosclerosis are of secondary importance in the development and evolution of rheumatic lung disease. This is based on our observation: 1, That in the large majority of cases the acute pneumonia or pneumonitis overshadows the collateral arteritis; 2, that the advanced arteriosclerotic lesion of the pulmonary artery seen often in association with mitral stenosis is uncommon in young rheumatic fever patients; 3, that interstitial pulmonary fibrosis in such young subjects is often already widespread and well advanced. These facts indicate that the pulmonary arteriosclerosis of rheumatic cardiopulmonary disease is a later development, and that despite its partial origin in inflammatory processes, it is largely subsequent to chronic pneumonitis and pulmonary hypertension. We hope to describe in detail the rheumatic pulmonary vascular lesions in a separate report, now in preparation.

Summary. 1. The characteristic pneumonopathy of acute rheumatic fever can be identified as the precursor of an equally characteristic pulmonary change seen often in chronic rheumatic heart disease.

2. An intervening subacute stage is featured, as is the late chronic stage, by impaired elasticity of the lung tissue.

3. Histologic studies indicate that this pulmonary lesion is a chronic interstitial pneumonitis, which like rheumatic myocarditis, is often accompanied by evidence of recurring inflammation.

4. One of its characteristic features is a hyperplasia of elastic tissue probably indicative of hypertensive strain in the fine pulmonary circulation.

5. This pulmonary change is not directly dependent on the presence of passive congestion or of mitral stenosis, since both of those factors may be absent or developed in variable degree. Passive congestion undoubtedly intensifies the interstitial fibrosis, but remains in our opinion a secondary factor.

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THE RÔLE OF MITRAL STENOSIS AND OF POST-RHEUMATIC PULMONARY FIBROSIS IN THE EVOLUTION OF CHRONIC RHEUMATIC HEART DISEASE.

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CHRONIC heart failure in rheumatic heart disease has been ascribed for years to the mechanical effects of mitral stenosis. It is generally accepted that mitral stenosis by retarding the onward flow of blood causes enlargement of the left auricle, later an increasing stasis in the pulmonary veins, creating thereby a state of chronic congestion, and hypertension in the pulmonary vascular circuit. The right ventricle undergoes hypertrophy and dilatation, and ultimately fails in its effort to overcome this pulmonary hypertension. This apparently is the pathogenesis of right heart failure with its congestive enlargement of the liver and peripheral venous stasis that is so characteristic of advanced rheumatic heart disease. In the majority of cases this would appear to be a satisfactory explanation. We have, however, in the last 5 years come to the conclusion that another factor aside from mitral stenosis itself is, at least in some patients, the major cause of right heart failure. This belief is based on a number of observations, which we wish to discuss in this report.

1. *The Normal Sized Left Auricle in Occasional Cases of Mitral Stenosis.* It has been thought by the profession at large, even by cardiologists and roentgenologists, that enlargement of the left auricle is an inevitable sequel to mitral stenosis and a measure of its severity. It is unquestionably the *usual* finding in patients who had long continued mitral obstruction. Nevertheless we have encountered in a series of 61 cases of mitral stenosis, 7 instances in which the left auricle was not enlarged (Fig. 1). While the entire group included varying grades of stenosis 4 of the 7 examples of non-enlargement of the auricle occurred in the presence of advanced stenosis of the type that is often described as "pure" mitral stenosis. The lesions were characteristically rheumatic. There was slight to moderate enlargement of the auricular appendage in some of these 7 cases, certainly not marked in any and not comparable with the enlargement of the right auricular appendage in the same hearts. In no instance was there associated congenital heart disease. A larger group was noted to have a comparatively slight degree of left auricular enlargement. This is probably within common experience, but is also challenging in view of the fact that mitral stenosis, usually advanced in these cases, is a development of many years' duration.

In the normal adult heart the length of the unopened left auricle

measured externally is practically one-half that of the left ventricle, the ratio of auriculo-ventricular length being 50 to 55%. In mitral stenosis, the length of the left auricle is usually two-thirds to three-fourths of the length of the ventricle and occasionally may equal it. All of the 7 cases herein stated to have normal sized left auricles accompanying mitral stenosis were within the normal ratio of auriculo-ventricular length. The age of these patients varied from 17 to 64.

It appears then that valvular obstruction is not the sole factor in the progressive left auricular dilatation of rheumatic heart disease. Unquestionably other factors, anatomic and physiologic, exert a marked local influence on the auricular structure. They cannot be discussed here, but we have concluded that mitral valve obstruction is only one of a number of such factors, that its importance in initiating the train of events leading to right heart failure has probably been exaggerated, certainly so in types of cases of mitral stenosis just described.

2. *The Significance of Right Ventricular Involvement in Rheumatic Heart Disease and Its Relationship to Mitral Stenosis.* It has been a matter of interest to us, as well as to others, that some people with mitral stenosis live considerably longer than the usual patient with rheumatic heart disease. The patients who reach the age of 45 constitute a larger group than is generally realized. Interesting statistical data has been recorded in previous papers.^{2,4,6,7,10}

We have observed that some patients with advanced mitral stenosis reached the 6th or 7th decade of life and at necropsy presented little or no evidence of congestive heart failure. This was in marked contrast with the large number of patients between the ages of 20 and 50 who having the same degree of mitral stenosis, presented the common evidence of right heart failure with congestive enlargement of the liver and peripheral venous stasis. The very different course in these two groups leads us to believe that mitral stenosis *per se* is not the factor that determines the outcome. The nature of a protective mechanism, if such actually exists, has been discussed by Levine and Fulton,⁷ who suggested that systemic hypertension prolonged life in mitral stenosis by producing dilatation of the obstructed mitral ring. The one pathologic change in the heart aside from mitral stenosis that is commonly present in the early development of chronic right sided insufficiency is the combination of hypertrophy and dilatation of the right ventricle, especially of the outlet portion (conus), which we believe to signify prolonged strain. It is our observation that this change is often absent, and when present, usually in mild degree in those cases of advanced mitral stenosis, who reach a normal life expectancy. We believe therefore that the chief factor which, barring complications, determines the severity of the course and the duration of life is the degree of right ventricular strain and not the degree of mitral stenosis.

An analysis of 30 cases of mitral stenosis, chosen at random, illustrated in a general way the clinico-pathologic importance of right ventricular hypertrophy and dilatation. The patients varied in age from 22 to 67. They could be generally divided into two groups on the basis of right ventricular strain as evidenced by the structural changes in that ventricle. The larger group consisting of 20 patients, average age 42.3 years, had chronic right heart failure and all of them showed moderate to marked hypertrophy and dilatation of the right ventricle (Fig. 2). The smaller group consisting of 10 cases with normal or practically normal ventricle (Fig. 3), did not have chronic right heart failure; their average age at death was 51 years; death was attributed to non-cardiac disease (5 cases), to left heart failure following coronary thrombosis (1), or following obstruction by ball-valve thrombus in the left auricle (1), to embolism secondary to auricular fibrillation (3).

Right ventricular hypertrophy, eventually strain and failure is the accepted rule in mitral stenosis. It is evident, however, that some patients may have severe mitral stenosis that is not necessarily followed by right ventricular strain for many years. Moreover, there appears to be a fairly proportionate relationship between longevity or an approach to it in mitral stenosis and the degree of freedom from right ventricular strain. The latter is a response to some form of pulmonary resistance, which evidently may or may not develop in the presence of mitral stenosis. The importance of this pulmonary factor is emphasized in the following chapter.

3. *The Existence of Chronic Right Heart Failure in Rheumatism Without Mitral Stenosis.* We have noted 3 instances of aortic stenosis unaccompanied by mitral stenosis, in which the clinical picture was essentially the same as that usually ascribed to the latter lesion alone, namely chronic right heart failure (Figs. 6 and 7). In all 3 instances, the valvular lesion was undoubtedly rheumatic; the age of these patients was 35, 36, and 51 years. Isolated aortic stenosis in a young or middle aged patient is uncommon from the anatomic standpoint; accompanied by the development of chronic right heart failure, it is distinctly uncommon, but the existence of such cases is of great significance in the attempt to trace the evolution of rheumatic heart disease. It becomes more evident that the cause of right heart failure in chronic rheumatic heart disease is more directly related to an impediment in the pulmonary circulation. This factor was present in each of these 3 cases; hypertrophy and dilatation of the right ventricle were associated with early pulmonary atherosclerosis and an altered consistency in the lung structure which obviously was the basis of increased intrapulmonary resistance and pulmonary hypertension in the entire absence of mitral stenosis and resultant back pressure.

4. *The Lesions of the Pulmonary Vessels. The Relative Immunity of the Pulmonary Veins in Mitral Stenosis Accompanied by Pre-*

dominant Right Heart Failure. In the chronic stage of rheumatic heart disease, pulmonary arterial involvement is often conspicuous, more so than in the early acute phases of rheumatic fever, and differing from the acute arteritis of the early involvement in that it consists largely of atherosclerosis, which is a degenerative reaction (Fig. 8). This development can be reasonably associated with the presence of a pulmonary hypertension, as pointed out by Moschowitz,^{8a} Parker and Weiss.⁹ The extent of the arterial degeneration is largely parallel on one hand with the degree of right ventricular hypertrophy and strain and on the other with the extent of a diffuse fibrosis in the lungs. We have just noted that pulmonary atherosclerosis and increased firmness of the lung structure were present in some cases of rheumatic heart disease in the absence of mitral stenosis (or any significant mitral valve lesion). It is also interesting that in patients with mitral stenosis, who reach middle or upper age with little or no cardiac disability, pulmonary atherosclerosis is usually slight (Fig. 5).

An interesting contrast to the state of the pulmonary artery and its branches in chronic rheumatic heart disease is afforded by the pulmonary veins. The relatively few observations concerning them are conflicting. Zinsser¹¹ found little involvement in the pulmonary veins in mitral stenosis. Brenner³ found sclerosis constantly in some degree in the small pulmonary veins, less so in the large veins.

LEGENDS FOR FIGS. 1 TO 9.

FIG. 1.—*A*, Normal sized left auricle with advanced mitral stenosis; the right auricle is moderately enlarged. *B*, Markedly enlarged left auricle, with advanced mitral stenosis. The degree of valvular obstruction was practically identical in heart, Fig. 1, *A*. Both hearts viewed from the rear.

FIG. 2.—Extreme cor pulmonale in rheumatic heart disease with mitral stenosis, viewed from left lateral aspect; severe chronic right heart failure in association with advanced interstitial pulmonary fibrosis and acute pulmonary arteritis. Right ventricular wall (*R*) measured 15 mm.; pulmonary artery (*P.A.*).

FIG. 3.—Absence of right heart hypertrophy and dilatation in a case of advanced mitral stenosis (see Figs. 4 and 5); patient aged 52, well until 6 weeks before death from auricular fibrillation and pulmonary embolism. Right ventricular wall (*R*) measured 4 mm.

FIG. 4.—Advanced mitral stenosis without right ventricular hypertrophy (see Fig. 3).

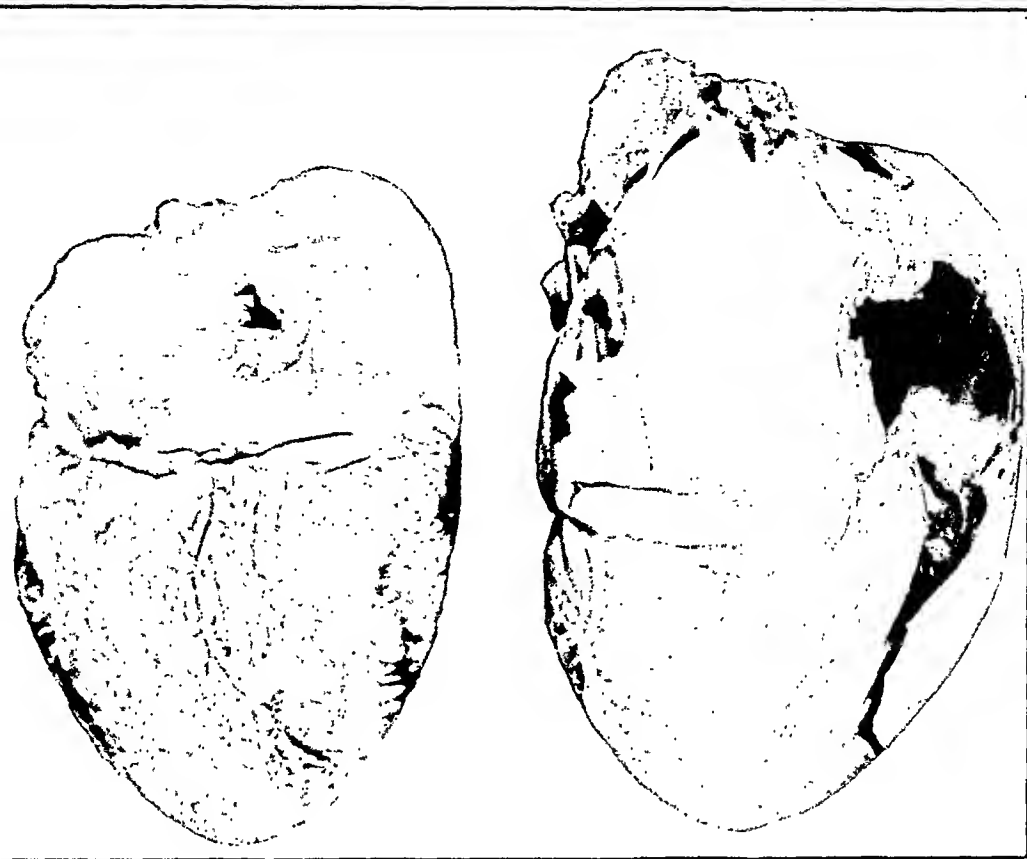
FIG. 5.—Absence of pulmonary arteriosclerosis in a case of advanced mitral stenosis (see Figs. 3 and 4). No significant sclerosis noted in small branches. The right ventricle was normal.

FIG. 6.—Hypertrophy and dilatation of right ventricle in a man, aged 36, with advanced post-rheumatic aortic stenosis and practically normal mitral valve (see Fig. 7). Death by chronic right heart failure. Right ventricular wall (*R*) measured 7 cm.

FIG. 7.—Slightly scarred but functionally normal mitral valve (see Fig. 6).

FIG. 8.—Marked pulmonary arteriosclerosis in association with mitral stenosis and chronic right heart failure.

FIG. 9.—Normal pulmonary veins in association with mitral stenosis and chronic right heart failure (see Fig. 8). The translucency of the normal pulmonary veins is lost in the photography.



A

FIG. 1

B

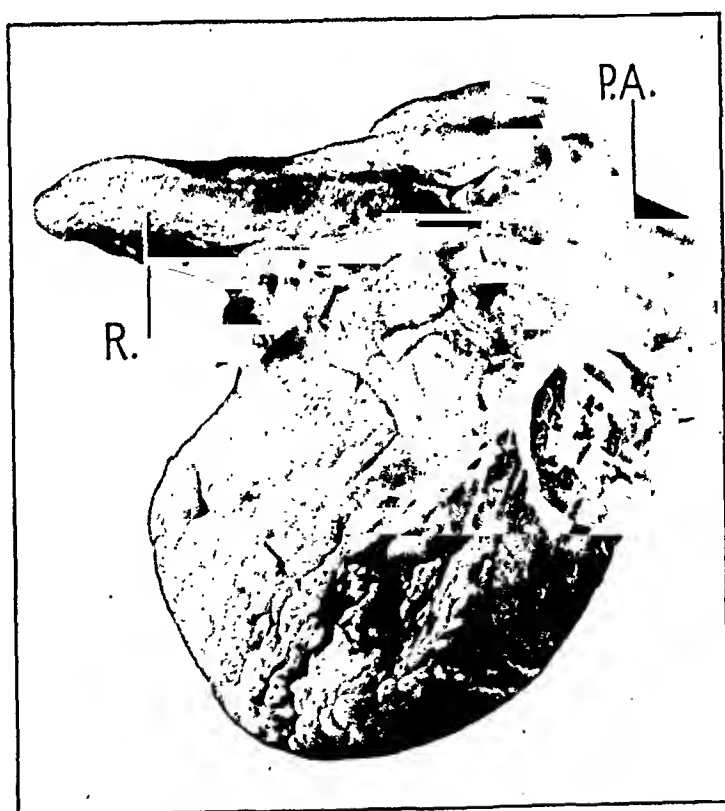


FIG. 2

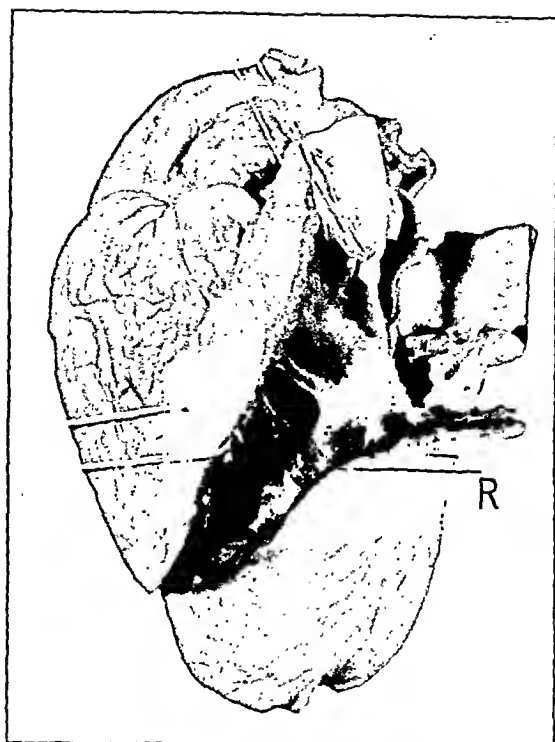


FIG. 3

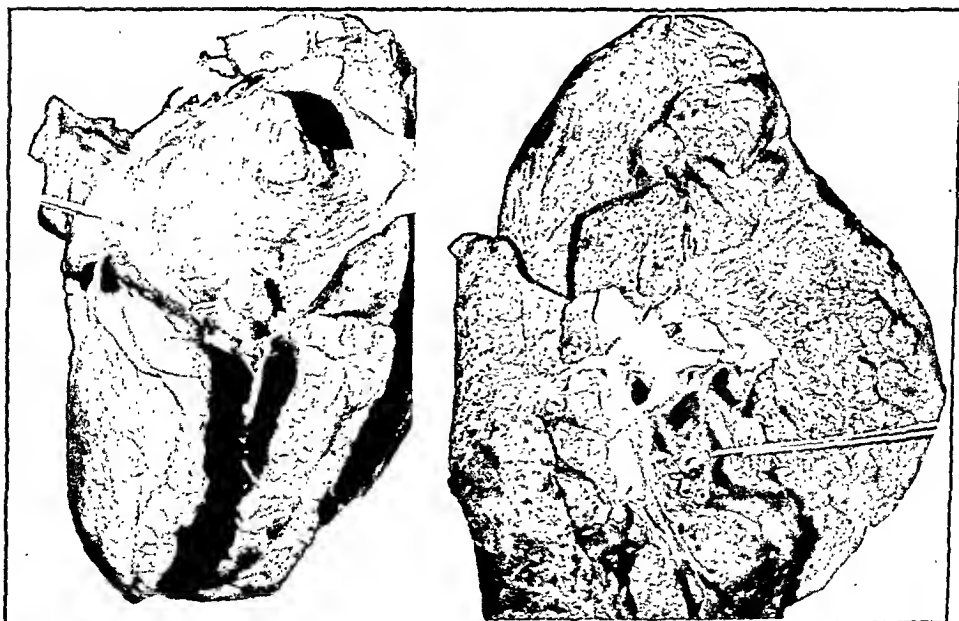


FIG. 4

FIG. 5

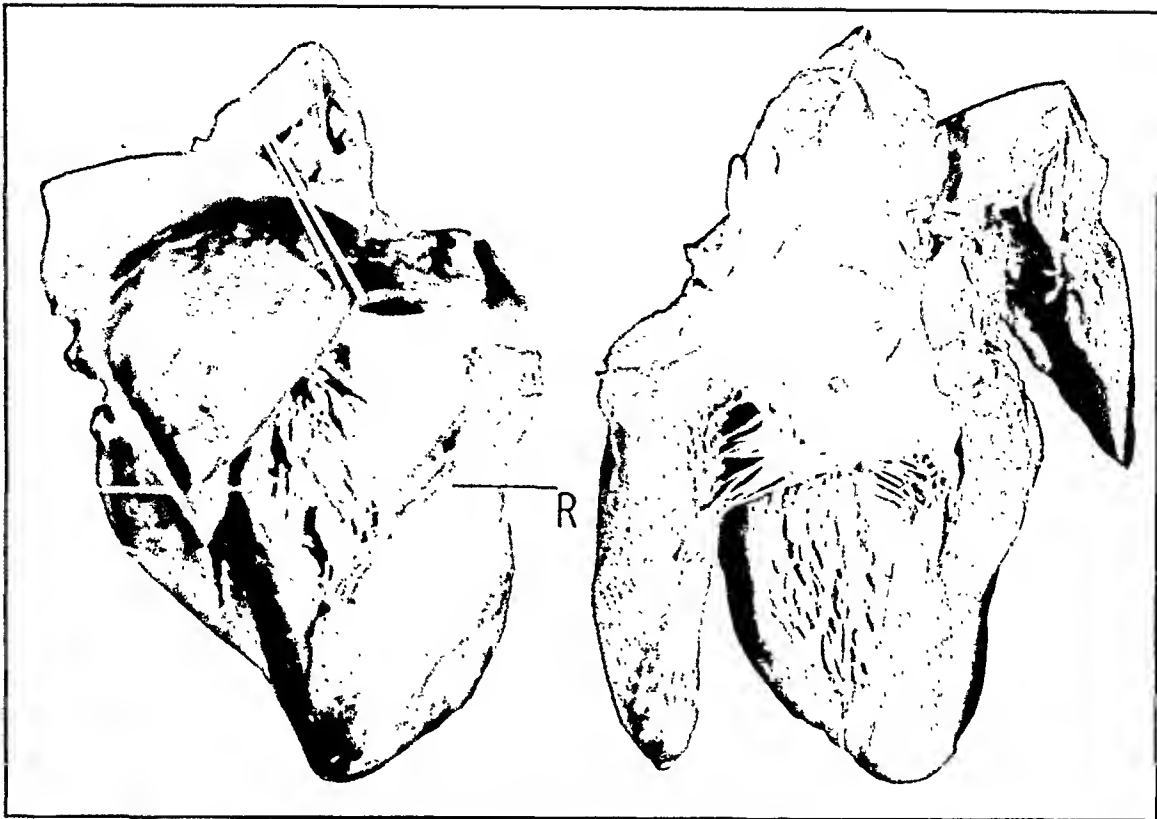


FIG. 6

FIG. 7



FIG. 8

FIG. 9

Indeed he found these changes in almost all lungs, in patients above the age of 10, regardless of the presence or absence of cardio-pulmonary disease. Some investigators found pulmonary phlebosclerosis in mitral stenosis increased with heart failure, but no reference has been made as far as we know as to the predominant type of failure in such patients: which is important because we have consistently found evidence of significant pulmonary phlebosclerosis in those patients who have suffered from predominant chronic left heart failure or at least a generalized type of failure regardless of etiologic considerations. Contrariwise, a fairly consistent necropsy observation is the relative immunity of the larger pulmonary veins in uncomplicated mitral stenosis with chronic right heart failure (Fig. 9). In such cases the contrasting pulmonary artery disease is often marked. In most of them some thickening of the venules usually slight to moderate was seen, similar to that noted by Bremner in practically all individuals, but there was a significant diminution of phlebosclerosis as one successively examined small, medium, and finally large sized branches of the pulmonary veins. This immunity was not so apparent with complicating left heart failure or when there was unusually marked left auricular enlargement and resulting dilatation of the orifices of the pulmonary veins. In such cases the existence of back stasis in the pulmonary veins was suggested by phlebosclerosis in large vessels which sometimes equalled that seen in patients with repeated myocardial infarction, decompensated hypertensive cardio-renal disease and other types of chronic left heart failure. Its slight development in uncomplicated mitral stenosis with ordinary auricular enlargement and predominant right heart strain strikes in our opinion at the theory of retrograde pulmonary venous hypertension originating at the mitral valve. The continuous obstruction of many years' duration usually associated with mitral stenosis ought to be productive of a pulmonary phlebosclerosis more intensive than seen with any other type of heart disease.

The Rôle of Chronic Pneumonitis in the Evolution of Rheumatic Heart Disease. The immediate cause of the pulmonary hypertension is, we believe, a diffuse interstitial lung fibrosis. Anoxic fibrosis (brown induration of the lung) secondary to heart failure and congestive stasis has long been known to pathologists, and it has always been assumed that the pulmonary changes in rheumatic heart disease were entirely of that type, and basically the result of obstruction at the mitral valve. The importance of pulmonary fibrosis in conjunction with pulmonary hypertension and mitral stenosis has been recognized. Moschcowitz (1930)^{8b} attributed the process, as others previously, to secondary capillary stasis and in the late stages to ischemia following advanced pulmonary arteriosclerosis. He employed the term "arterio-capillary fibrosis" (Gull and Sutton) and showed a similarity of the pulmonary and renal

capillary lesions in their association with hypertension. Parker and Weiss⁹ in the latest work on this subject also emphasized the fibrotic changes in the capillary vessels and alveolar walls and their effect on gaseous exchange, but they likewise considered these lung changes to be a secondary result of chronic left heart failure ("back pressure"). In their case of mitral stenosis they thought that right heart involvement was a terminal event due to a malignant pulmonary hypertension which had developed rapidly toward the end of life.

The observations herein recorded make it difficult for us to apply the theory of back pressure and stasis to all cases of mitral stenosis without reservation. There is reason to believe that in some patients (and possibly this in time will be found applicable to others) the essential cause of the failure is not in valvular obstruction but rather in an important and independent structural change in the lung. This phenomenon is in the beginning a direct result of rheumatic fever, a pneumonitis leading often to a widespread fine interstitial fibrosis, which may with recurrences of the inflammatory reaction become progressively severe. The transition from the acute rheumatic lung lesions to the later stages of post-inflammatory fibrosis has been recently reported.^{5b} The development of pneumonitis in rheumatic fever is concurrent with cardiac involvement; nevertheless, we have seen instances especially in children, where the almost inevitable mitral valvular lesion was comparatively slight, far from actual stenosis and yet at the same time pneumonitis had already developed into the "rubberoid" lung. In these early victims of rheumatic disease the obstructive pulmonary factor was already evident, in the early hypertrophy and marked dilatation of the right ventricle. It may be pointed out that chronic congestive heart failure of the type associated with paroxysmal dyspnea, and recurring pulmonary edema is seldom present in such young patients.

The writer has observed the presence of cardiac murmurs in the pulmonary area in children after an attack of rheumatic fever in whom no murmurs were previously heard. A short but sometimes rough systolic murmur followed by marked accentuation of P-2 are not infrequent under such circumstances; such murmurs in the area of "auscultatory romance" are difficult to assess. The fact that the development of mitral stenosis occurs at least a few years after the early attacks of rheumatic fever¹ leads us to believe that some of these murmurs in the pulmonic area may be related to increased pulmonary tension.

In the later stages of chronic rheumatic heart disease the development of left ventricular failure in numerous patients adds to the pulmonary obstruction by the imposition of passive congestion on a vascular circuit already handicapped by post-inflammatory interstitial fibrosis. In this connection the extent of the valvular ob-

struction is apparently of little importance as long as the integrity of the left ventricle is maintained. A normal or well functioning left ventricle gives the right ventricle opportunity to meet whatever obstruction exists in the pulmonary capillary bed that has resulted from the original inflammatory process. A constant passive congestion of the lungs has been assumed to exist in all patients with mitral stenosis. That this may be a fallacy was discussed by us in a previous paper,⁴ in which attention was called to the interesting and not infrequent necropsy finding of the "dry lungs" in chronic rheumatic heart disease. Those patients who are ambulatory and completely compensated and with characteristically normal or even small left ventricle show no Roentgen or clinical evidence of passive congestion of the lungs.

The heart in rheumatic disease cannot be considered alone in reference to circulatory efficiency. The pulmonary status assumes in our opinion equal importance. The extent of the intrapulmonary blockade and the ability of the right ventricle to cope with it determines the course and prognosis of each case. The importance of recurring myocarditis is recognized; in our opinion, it hastens but scarcely alters the general pattern of cardiac failure in adult patients. The same may be said of auricular fibrillation, unless fatal embolism supervenes. The situation is aggravated of course if and when the left ventricle fails. Aside from recurring inflammation, there are structural changes in many rheumatic hearts that lead to the complication of left ventricular strain and ultimately generalized failure (serious aortic valvular disease, adherent pericardium, the hypertrophy and strain of essential systemic hypertension). In their absence, left ventricular failure is usually a sub-terminal event coming on many years after the development of right ventricular strain.

It is true that the majority of patients with rheumatic heart disease have no history of acute pulmonary involvement at any time. It was pointed out, however, that in many instances a subtle sub-clinical pneumonitis had occurred and was discovered only at necropsy.^{5a} The mitral valvular lesion and the interstitial pulmonary fibrosis are not in a given case parallel in extent with each other. It is very likely that in many patients a comparatively mild pulmonary lesion disappears in early life while the mitral valvulitis persists and progresses in the later years. Thus patients are occasionally seen with advanced mitral obstruction, even beyond middle age, in whom the parenchymal lung lesion is slight.

Summary. We have discussed the probability: 1, that mitral stenosis in some patients is in itself not the sole or possibly even an important factor in the causation of the chronic right heart failure which characteristically terminates chronic rheumatic heart disease; 2, such failure may occur even in the absence of significant mitral valvular dysfunction; 3, the key lesion in this particular

type of patient is the association of an intrapulmonary lesion with right ventricular strain; 4, the intrapulmonary lesion is a diffuse fibrosis that at least in its beginning is a direct result of rheumatic pneumonitis; 5, the factor of passive pulmonary congestion becomes important with the development of left ventricular failure which may or may not occur.

The protocols of the cases of mitral stenosis with normal sized left auricle and also of those concerned with the structural changes in the right ventricle have been omitted. They are listed separately and are available on application to the author.

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THE SITE OF ACTION OF THE RENAL PRESSOR SUBSTANCE.*

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THE experiments to be reported were undertaken in order to investigate the mechanism of action of the renal pressor substance (Tigerstedt's "renin").

Method. The observations were made on heparinized rats which were anesthetized with sodium pentobarbital. The pressor substance was prepared by treating ground renal cortex with alcohol and extracting the precipitate with water as described by Merrill, Williams and Harrison.³ Various structures were removed, destroyed or separated from the circulatory systems of the test animals, and the active material was then injected through an aortic cannula. The cannula was equipped with a side connection through which blood pressure was measured with a mercury manometer. The rises in blood pressure due to the volume of fluid injected were determined by administering equal volumes of 0.9% sodium chloride solution. In the first series of experiments no attempt was made to determine whether these procedures altered the degree of pressor response but simply whether they abolished it.

* This investigation was aided by a grant from the Josiah Macy, Jr., Foundation.

The Influence of the Nervous System. In one group of experiments a tracheal cannula was inserted, artificial respiration was administered, and the connections between the brain and the remainder of the body were destroyed by clamping all the cervical structures except the trachea in the lower part of the neck. The clamp crushed the cord, the vagus nerves and the blood-vessels. Each of 7 rats so treated exhibited markedly greater response to "renin" than to saline. The response of these animals was usually greater than that observed in rats with intact cords, the difference probably being due to the low initial pressure which followed destruction of the spinal cord. In a second series of experiments, the spinal cord was exposed in the neck and the lower portions of it were destroyed by passing a wire down the vertebral canal, artificial respiration being maintained through the tracheal cannula. Each of 5 rats so treated displayed a well-marked pressor response to renin.

These observations are in agreement with those of previous workers^{1,4} in showing that the rise in blood pressure produced by the renal pressor substance is independent of central nervous system influences. The results do not, however, demonstrate a direct peripheral vasoconstrictor action of this substance, for it is conceivable that the effect might be due to some substance formed in other parts of the body and liberated by the injection of renal extract. In order to study this question further experiments were done.

Effect of Removal of Various Organs From the Circulation. The possibility that the pressor effects of renin could be due to substances formed in the hypophysis was excluded by the experiments already mentioned, in which the structures in the lower part of the neck were tightly occluded by a clamp. Since under these conditions the venous return from the hypophysis was blocked it is clear that secretions from these organs could not have been responsible for the pressor effect.

In order to study the possible rôle of the lungs comparisons were made of the effect of intravenous and intra-aortic injections. It was found that the initial depressor effect produced by renal extract was usually more pronounced when the intravenous route was employed. This result was interpreted as meaning that our extracts probably contained peptones, which have been shown by Mauntner and Pick² to cause constriction of the pulmonary vessels. (The method of preparation of the extracts makes it unlikely that they could contain histamine, which may have a similar action on the pulmonary vessels.) When allowance was made for the greater depressor effect no significant difference was found between the effects of intra-aortic and intravenous administration.

The liver was excluded from the circulation by diverting the portal blood into one of the renal veins with a curved cannula, the

hepatic artery being ligated. Only two successful preparations were obtained. Both of these rats showed a well-marked pressor response to renal extract, the effects being greater—probably because of the lower initial blood pressure—than those obtained on control animals with intact livers.

Removal of the spleen—1 rat—and of the pancreas—5 rats— did not abolish the pressor effect which was about the same as that obtained on untreated animals.

In 6 rats the adrenal glands were removed immediately before the injection. All of these animals showed normal responses when renin was administered.

In 10 experiments the renal pedicles were alternately clamped and released during injections of renal extract. Removing the kidneys from the circulation did not alter the pressor effects.

These observations suggest that the rise in blood pressure produced by renin is due to a direct local effect on the vessels. The question was studied further by observing the effect of the extract administered locally on the perfusion rate through the leg. In some experiments, a cannula pointing toward the head was inserted into the proximal part of the left common iliac artery, the aorta being clamped just above its bifurcation during the measurements of the perfusion rate and released between such measurements so that the blood supply was maintained to the right leg except during the time when the rate of flow through the right common iliac artery was being determined. In other experiments, a cannula pointing toward the foot was placed into the femoral artery of the excised leg, separated completely from the body. The results obtained with both types of experiment were similar and are illustrated in Figure 1. The administration of renin was followed by well-marked vasoconstriction in the vessels of the leg, although the duration of the effect—5 to 10 minutes—was usually considerably less than the usual duration—15 to 30 minutes—of the pressor response in intact animals. Whether this difference is to be ascribed to the fact that the pressor substance was rapidly washed out of the leg by the perfusion fluid or to some other reason is uncertain, but the experiments do indicate clearly that renin causes local vascular contraction, independently of the nervous system, and that the pressor effect is a direct one in the sense that it is not due to the liberation of pressor substances from other parts of the body but is dependent on the effect of renin itself on the blood-vessels.

The experiments which were mentioned above in which it was shown that clamping the renal pedicles did not alter the response of the animals to renal extract seem, at first sight, to be contrary to those of Tigerstedt and Bergman,⁴ who found that bilateral nephrectomy caused rabbits to become more sensitive to renin. They attributed this to the inability of such animals to excrete

renin. In order to investigate the reason for the difference between their results and ours, further experiments were done, the kidneys being removed from a series of rats, which were compared 2 or 3 days later with control animals as regards sensitivity. These experiments (Fig. 2) indicated clearly that rats which have had their kidneys removed 2 or 3 days previously are more sensitive to renal extract than are normal animals. On the other hand, it was found that nephrectomy or clamping the renal pedicles immediately before the injection did not increase the sensitivity of the animals (Fig. 2). The results confirm the findings of Tigerstedt and Bergman, but do not support their assumption that the difference in sensitivity is due to failure of the nephrectomized animals to excrete the pressor substance. The reason for the increased sensitivity of the latter rats is not clear at the present time and needs to be studied further.

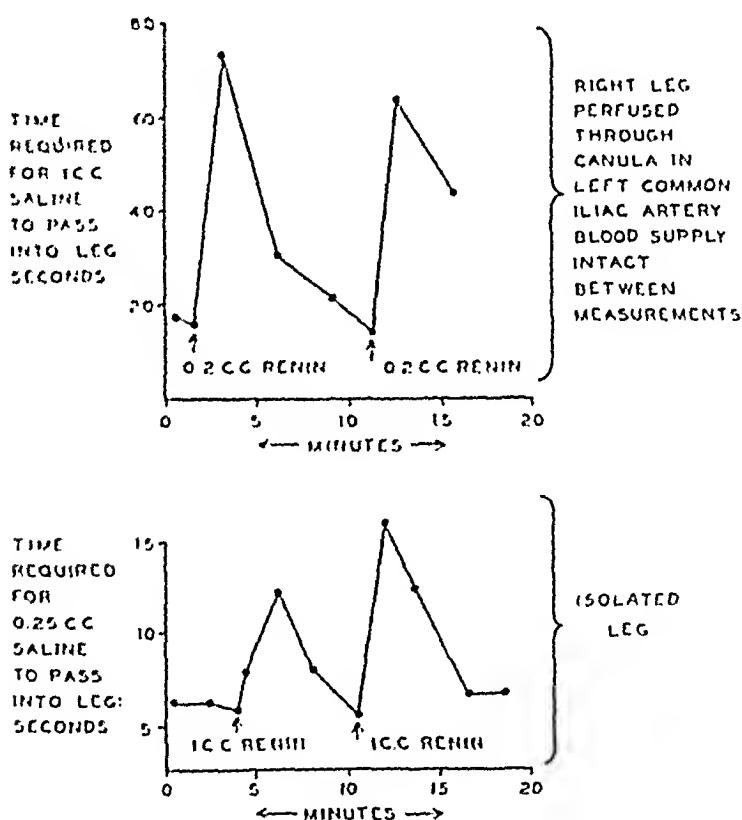


FIG. 1.—The two experiments illustrate the local vasoconstrictor action of renin as shown by a decrease in the perfusion rate through the leg.

The experiments indicate that the renal pressor substance has a direct vasoconstrictor action, which occurs independently of structures other than the blood-vessels. The pressor response is not abolished immediately after removal of various structures. However, removal of the kidneys does modify the action of the pressor substance provided that the animal has been deprived of the renal

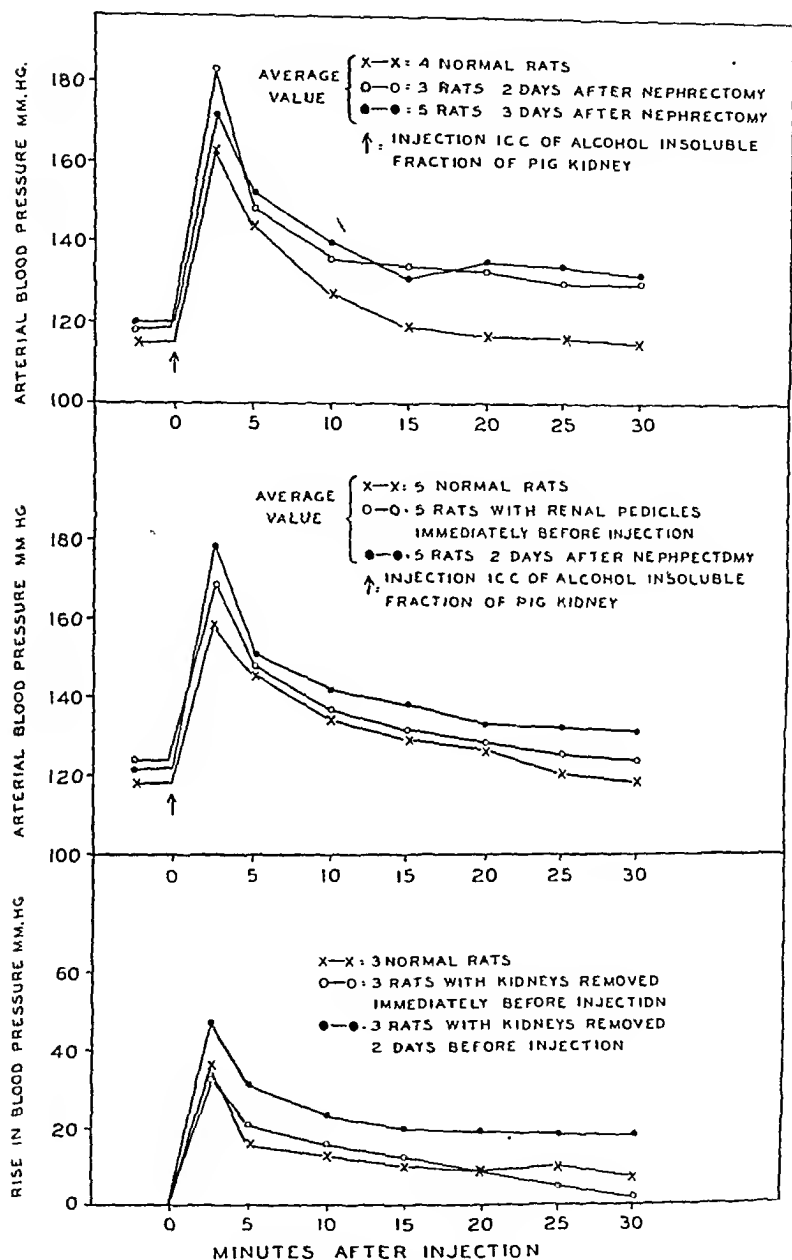


FIG. 2.—Two or three days after bilateral nephrectomy the sensitivity of the animals to renin was markedly increased, particularly as regards the duration of the effect (A, B, C). Ligation of the renal pedicles immediately before the injection of renal extract had practically no effect on the response to renin (B). Likewise the response was not altered immediately after removal of the kidneys (C).

tissue for a sufficiently long period. It seems quite possible that several days after the removal of other organs the effect might also be modified even though the response is not changed immediately after the exclusion of these structures. Experiments aimed at testing this hypothesis are now in progress.

Summary. Injection of the renal pressor substance—renin—caused rise in blood pressure after destruction of the spinal cord, and after exclusion of the hypophysis, adrenals, pancreas, liver and kidneys from the circulation. A vasoconstrictor effect of this substance was demonstrated in the isolated leg. Although the character of the pressor response was not altered by removing the kidneys immediately before the injection, it was found that the height and duration of the rise in blood pressure were increased in animals which had been subjected to nephrectomy 2 or 3 days previously.

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THE INSENSIBLE LOSS OF WATER IN DIABETES INSIPIDUS.*

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SCANT attention has been paid to the measurement of the insensible loss of water in diabetes insipidus in spite of the fact that this loss forms an important item in the total water balance. Early studies were published by Strubell⁹ and Veil;^{10a,b} but their technique was inaccurate and their results discordant. In normal subjects, the insensible loss of water is a function of the total metabolism⁸ and appears to be independent of the less extreme dislocations of the water exchange. Water diuresis, and antidiuresis produced by the injection of pituitrin, are usually found to have no influence on the insensible weight loss,^{1,2,3} although Manchester and co-workers⁶ reported an altered loss under these conditions. In patients with diabetes insipidus it is possible to extend these observations, as one can cause rapid and large shifts in the intake and output of water by the administration and withdrawal of pituitrin. Laviertes⁴ recently reported that the insensible loss of weight of such a patient

* Reported to the Chicago Society of Internal Medicine on November 22, 1937.

varied from 840 to 1644 gm. a day over a period of 9 days, during which the volume and osmotic pressure of the body fluids were varied greatly by the use of pituitrin and by changes in the salt intake. He observed no correlation between the variations in the insensible loss and the changes produced in the body hydration.

Furthermore, to understand the disturbed physiology of diabetes insipidus it is important to know whether or not the insensible loss of water differs essentially from that found in normal individuals. Such a difference would suggest that the metabolic anomaly in that disease is more widespread than one having to do solely with the control of the urine volume by the kidneys.

Clinical Abstracts.* SUBJECT K. was a 31-year-old housewife of Hungarian extraction who complained of amenorrhea, polyuria, and an increase of 25 pounds in weight, all within the few months previous to the observations recorded in this paper. The routine physical examination was negative, as were the neurologic examination, visual fields, serologic tests, spinal fluid findings, and the Roentgen ray of the region of the *sella turcica*. Except for the low specific gravity, routine examination of the urine was negative.

SUBJECT L., a 21-year-old, unmarried girl, evidently had a congenital type of diabetes insipidus. Her polyuria and polydipsia started early in life, and her mother had suffered from similar symptoms. Routine physical and neurologic examinations were negative, as were her visual fields, serologic tests and Roentgen ray of the *sella turcica*. Her urine usually contained a faint trace of albumin, too little to quantitate accurately; the urinary sediment was negative.

Methods. The insensible loss of water of each subject was determined for a number of consecutive days while the diabetes insipidus was alternately controlled with pituitrin and allowed to go unchecked. Pituitrin was driven intramuscularly in doses of 0.5 cc. of the obstetrical preparation on the days designated by a P in the date column of the tables. In determining the insensible loss of water the technique of Newburgh, as described in his several papers,⁸ was carefully followed. The chair balance used to weigh both subject and urine specimens had a sensitivity of 1 to 5 gm., depending on the load; the food consumed and the stools were weighed on a smaller balance to the nearest gram. The subjects were hospitalized and instructed to establish as nearly as possible a constant plane of activity, to avoid sensible perspiration or undue cooling, and to refrain from bathing. The term ($\text{CO}_2 - \text{O}_2$) which is subtracted from the insensible loss of weight to obtain the insensible water loss (Table 1) was calculated as described by Newburgh.⁸ No allowance was made for the heat expended in warming to body temperature the large volume of water the subjects drank, as it was found that on an extreme day, March 25, when Subject L. consumed over 10 liters of water, such a correction would have changed the term ($\text{CO}_2 - \text{O}_2$) by only 4 gm.

Insensible Loss of Water. In Table 1, Column 4 gives the values for the daily insensible water loss, while Column 5 shows the effect of the pituitrin injections on the urine volume.

In the case of Subject K., the polyuria and polydipsia which

* We are indebted to Dr. Allan T. Kenyon for the opportunity to study both these cases.

accompanied the withdrawal of pituitrin was associated on 3 out of 4 days with a somewhat decreased insensible loss of water. From Table 2 it will be seen that on 2 of these days, December 13 and December 17, a strongly negative water balance occurred, while the third day, December 18, marked the recovery from an especially severe dehydration. As Subject K. weighed 80 kg., a loss of 3 liters would represent a loss of 5% of her total body water (calculating the latter as 70% of her body weight). It is possible that such a marked dehydration may cause a decrease in the insensible loss of water. Manchester, Husted and McQuarrie⁶ reported that the insensible weight loss decreased in a manner parallel to the dehydration they produced in epileptic children; but Levine and Wyatt⁵ failed to observe such a correlation. Newburgh and Johnston⁷ and Hall and McClure² agree that a dehydration in which less than 6% of the total body water is lost has no effect on the insensible loss of water of normal subjects, while in the experiments of Hall and McClure a more severe dehydration was associated with a decreased insensible loss.

TABLE 1.—THE INSENSIBLE LOSS OF WATER IN DIABETES INSIPIDUS.

Date, (1)	Insensible weight loss, (2)	CO ₂ —O ₂ , (3)	Insensible water, (4)	Urine, (5)
<i>Subject K.</i>				
12/11 P*	870	82	788	4,055
12 P	832	82	750	3,322
13	705	82	623	8,180
14	811	82	734	5,117
15 P	859	82	777	3,001
16 P	827	82	745	3,022
17	630	82	548	10,265
18	702	82	620	6,692
<i>Subject L.</i>				
3/18 P	1247	71	1176	2,600
19 P	1212	71	1141	1,408
20 P	1156	97	1059	4,558
21 P	1209	97	1112	3,008
22	1097	99	998	7,180
23	1135	99	1036	8,911
24	1092	99	993	9,884
25	1054	99	955	10,520
26 P	1109	99	1010	3,935

* P in Column 1 indicates that pituitrin was given that day.

We are not at all sure that dehydration accounts for the decrease in K.'s insensible water on the days in question. She felt very badly when pituitrin was withdrawn and may, as a result, have been less active, just as was the normal subject of Newburgh and Johnston when he was undergoing dehydration. Also, the change

in the insensible water is small enough in magnitude to make it difficult to be sure of its significance. Thus from Newburgh's most recent work,⁸ in which the energy output calculated from the insensible loss of water is compared with that observed by simultaneous indirect calorimetry in the respiration chamber, it is clear that in an individual 24-hour period the insensible water loss may not show quite its usual relationship to the total expenditure of energy.

We believe that a reduced total metabolism resulting from a decrease in activity accounts for the fact that Subject L.'s insensible losses were uniformly about 10% lower during the second period of 4 days when pituitrin was withheld than they had been during the first 4 days of pituitrin administration. Subject L. had led a very active life and slowly accustomed herself to the hospital régime.

Withdrawal of pituitrin, which leaves the diabetes insipidus uncontrolled, has, then, at most, only a minor effect on the insensible water loss, which latter bears its usual close relationship to the total metabolism.

TABLE 2.—ESTIMATED WATER BALANCE IN 2 CASES OF DIABETES INSIPIDUS.

Date. (1)	Estimated.			Observed weight change. (5)
	Intake. (2)	Output. (3)	Balance. (4)	
Subject K.				
12/11 P	3,231	4,806	-1575	-1510
12 P	4,940	4,037	+ 903	+ 983
12/13	6,092	8,871	-2779	-2973
14	8,305	5,803	+2502	+2549
12/15 P	4,399	3,729	+ 670	+ 744
16 P	3,691	3,718	- 27	+ 102
12/17	7,624	11,423	-3799	-4075
18	7,779	7,311	+ 468	+ 463
Subject L.				
3/18 P	4,751	3,844	+ 907	+ 794
19 P	3,547	2,555	+ 992	+ 882
20 P	4,612	5,641	-1029	-1066
21 P	4,748	4,168	+ 580	+ 532
3/22	7,473	8,157	- 684	- 708
23	10,542	9,970	+ 572	+ 563
24	11,082	10,949	+ 133	+ 138
25	11,729	11,539	+ 190	+ 210
3/26 P	5,169	4,984	+ 185	+ 203

Water Balance. The principal change observed in discontinuing the administration of pituitrin to a subject with diabetes insipidus is the marked increase in the water consumed and in the urine voided. These two items of the water balance, together with the insensible water, were carefully measured in our observations. The

other terms in the fluid exchange, namely, the amounts of water in the urine and stool, were not determined, but calculated indirectly, and the resulting estimated water balances are presented in Table 2. The water intake, Column 2, is the sum of the water drunk, plus the water content of the food derived from standard tables, plus the metabolic water calculated in the usual way from the metabolic mixture. The figures for the water output in Column 3 represent the sum of the insensible water plus the water excreted in the urine and stool (the last item estimated from the generalization that fresh stool contains about 80% water). It is well recognized that for short periods of time and when a maintenance diet is fed, changes in the body weight closely approximate the water balance. Thus the figures in Column 5 serve as a check on the estimated balance values in Column 4.

It will be noted that Subject K. showed a very unstable balance with a tendency to frequent dehydration while Subject L. was much less variable in her water exchange. She had had her diabetes insipidus all her life and never resisted her thirst whereas Subject K. had suffered only a few months, was extremely dissatisfied with her condition, and undoubtedly attempted to control her polyuria by drinking less.

Summary. We have determined the daily insensible loss of water in 2 cases of diabetes insipidus in which the water exchange was subjected to large fluctuations by the administration and withdrawal of pituitrin. The insensible water loss is of the same order of magnitude whether or not pituitrin is injected and evidently bears in diabetes insipidus its usual close relationship to the total metabolism. The variations observed in the insensible loss of water were considered to be due to changes in activity rather than to dislocations in the water exchange, although the changes were of small enough magnitude to make the distinction difficult with the methods available.

Estimated water balances were calculated from the metabolic data. One subject, K., showed a very labile balance with a tendency to dehydration, while L. was much more stable in regard to her water exchange.

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OBSERVATIONS ON THE CONTINUED USE OF PROTAMINE ZINC INSULIN IN PATIENTS WITH SEVERE DIABETES MELLITUS.

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PROTAMINE insulin* in the treatment of diabetes mellitus was first reported in this country in January, 1936.^{2,5} Although this method of therapy has now been in use for almost 2 years and there have been numerous published reports, there is little specific information, even in the more recent papers,^{1,3,4,6,7} as to the number of cases treated, the duration of the diabetes, the previous soluble insulin requirement in units and doses, and whether it was necessary to continue soluble insulin in conjunction with the protamine. Furthermore, objective data on the effect of protamine insulin on the clinical condition of the patient, *i. e.*, weight changes, tendency to glycosuria or insulin shock, and so forth, are meager. It is understandable that in the earlier publications follow-up records were not possible; but even the more recent reports still give little data on the effect of the continued use of protamine zinc insulin. In the earlier reports of protamine insulin most of the attention was given to the level of the blood sugar in the patients treated. Blood sugar curves were done on patients with protamine insulin and it was obvious that this form of insulin had the ability to reduce the blood sugar for a more prolonged period than did soluble insulin.^{5,7} It was our experience in observing the effects of protamine insulin on the blood sugar for 24 hours at 2-hour intervals that a somewhat more constant level of blood sugar was maintained than with soluble insulin, although considerable variations were still present. Very little attention was paid to the glycosuria, although this is probably a more accurate index of the status of the diabetic patient throughout the day.

We are reporting a group of 20 patients, 16 of whom have been studied for periods of not less than 8 months while receiving protamine zinc insulin. The other 4 were observed for 1 to 2 months

* The protamine zinc insulin used in this study was Protamine Zinc Insulin Lilly.

in the hospital, at the end of which time protamine insulin was discontinued owing to the fact that it was impossible to prevent a significant degree of glycosuria. All of the patients reported had previously been under our observation and treatment in the clinic for an equal or longer period of time on soluble insulin.

Observations. In this group of patients 12 were males and 8 were females. The ages varied from 9 to 70 years; 6 patients were between 9 and 16 years, 4 between 20 and 25, 5 between 30 and 40, 4 between 40 and 50 and 1 patient was 70 years of age. All of these patients had had diabetes mellitus for more than 2 years. The average duration of the disease was 6 years. The details of the patients are given in Table 1.

TABLE 1.—DATA ON 20 CASES STUDIED.

Case No.	Age in years.	Sex.	Duration of diabetes, years.
1	40	F	14
2	50	F	7
3	38	M	2½
4	41	M	5
5	34	F	14
6	11	F	2
7	33	F	6
8	24	F	3
9	25	M	10
10	14	F	4
11	35	M	9
12	16	M	4
13	20	M	4
14	21	M	3
15	37	M	8
16	9	F	5
17	10	M	4½
18	70	M	13
19	12	M	6
20	52	M	4

The procedure used in studying these cases was as follows. Each patient was hospitalized and the soluble insulin requirement and diet as observed in the clinic were checked. When we were satisfied how much of the soluble insulin was required to prevent glycosuria, protamine zinc insulin was begun. During the first period of treatment with protamine the soluble insulin was gradually reduced and when possible was discontinued. Urines were collected for the entire 24 hours in 4 fractional periods; from after breakfast to before lunch, from after lunch to before supper, from after supper to 8 P.M. and from 8 P.M. to before breakfast, which was usually 8 A.M. Frequent blood sugars were taken during this period of adjustment and in several cases 24-hour blood sugar determinations were made every 2 hours during the initial period of adjustment. These 24-hour blood sugar determinations are not reported because our findings were similar to those of other observers.

Results. Table 1 gives the age, sex and duration of the diabetes in the patients studied. In Table 2 is summarized the soluble insulin prior to protamine therapy, the insulin both soluble and protamine during the early period of protamine therapy and the final insulin requirement, both soluble and protamine, at the end of the period reported. We have designated the time during which the patients responded fairly well to protamine insulin therapy as the "early period." As the average of this was 6 months, we have also reported in Table 2 the status at 6 months of the patients who continued to do well on protamine insulin for longer periods.

TABLE 2.—INSULIN REQUIREMENTS BEFORE AND DURING PROTAMINE INSULIN THERAPY.

Case No.	Daily units.	No. of doses daily.	Time observed in months.	Total daily protamine insulin.		Added daily regular insulin.		Time in months.	Total daily protamine insulin.		Added daily regular insulin.		Total duration protamine therapy in months.	Present status.
				Units.	No. of doses.	Units.	No. of doses.		Units.	No. of doses.	Units.	No. of doses.		
1	145	4	62	95	2	35	2	7	120	2	20	1	16	Discontinued
2	80	4	49	32	2	0	0	3	40	2	0	0	16	Same
3	85	4	5	37	2	14	1	11	30	1	30	2	17	Same
4	60	4	5	72	2	0	0	8	20	2	60	2	16	Same
5	85	4	45	45	1	10	1	6	45	1	10	1	13	Same
6	45	3	15	25	1	10	1	7	10	1	55	2	10	Discontinued
7	50	3	37	25	1	10	1	6	25	1	10	1	10	Same
8	75	4	36	45	2	25	2	7	30	1	30	2	10	Discontinued
9	75	3	4	40	2	15	2	3	20	1	25	2	8	Same
10	60	3	28	50	2	10	1	8	25	1	25	2	14	Same
11	50	3	45	60	2	0	0	9	60	2	12	1	15	Same
12	100	4	31	40	2	30	2	8	30	2	0	0	23	Same
13	65	4	24	30	2	0	0	7	40	2	0	0	14	Same
14	110	4	36	45	2	35	2	6	90	2	38	3	19	Same
15	65	4	72	53	2	0	0	6	50	2	5	1	13	Discontinued
16	65	4	60	30	2	15	2	3	40	2	30	3	8	Discontinued
17	40	4	36	25	1	10	1	2	25	1	15	1	2	Discontinued
18	65	4	48	30	1	20	1	2	30	2	45	2	2	Discontinued
19	40	3	3	40	2	0	0	1	25	1	0	0	1	Discontinued
20	85	4	53	70	2	20	1	1	75	2	20	1	1	Discontinued

Of the 20 patients treated, 4 were never successfully transferred to protamine insulin (Cases 17, 18, 19, 20) and the attempt was discontinued at the end of 1 or 2 months. These 4 patients were hospitalized during this entire period of observation and various arrangements in the amounts of protamine insulin, the time of its administration, as well as combinations with soluble insulin, were tried without success.

In the remaining 16 patients protamine insulin was used for periods varying from 8 to 23 months. In 5 of these (Cases 1, 6, 8,

15, 16) it was necessary to discontinue the protamine insulin because it became impossible to control the glycosuria without producing insulin reactions, the sequelae of which often incapacitated the patients for periods of from 24 to 48 hours. The shocks, unlike those following soluble insulin, were accompanied and followed by severe headache which was uninfluenced by the administration of carbohydrate, and which often lasted for several days. In 2 cases these shocks were accompanied by mental symptoms. All of these patients were on both protamine and soluble insulin, the total amounts varying from 55 to 140 units. The total amount of protamine insulin did not exceed 50 units in 4 of the cases, but in the 5th case 120 units were given. Of these 5 patients, 3 did fairly well for the first 6 months but the other 2 were never really adequately controlled.

In each of the 3 periods the total units of insulin required daily, the number of doses and the time over which the observations extended are recorded for each patient. Table 3 compares the status of the patient while on soluble insulin with his final status on protamine insulin and from this table one can readily see the patients in whom the diabetes was controlled. We have also noted in this table the tendency to shock, coma or infections during the period when the patient was on protamine insulin as compared to the period when he was on soluble insulin alone.

Of the 11 patients continued on protamine insulin, 8 (Cases 3, 4, 5, 7, 9, 10, 11, 14) still require additional soluble insulin varying from 10 to 60 units. In this group of patients, the number of injections of insulin required daily have decreased from 4 times on the soluble insulin to 1 or 2 on the combination, with the exception of 1 case who still requires 3 injections daily. Although this means that the patient needs to take insulin only twice during the day, the number of injections he has to make remains the same, as we have found it inadvisable to inject soluble insulin and protamine insulin at the same site. The total combined amounts of insulin in these cases were decreased in 5 of the patients. The decrease varied from 10 to 30 units daily. In 1 case there was no significant change in the total amount of insulin, and in 3 patients the combined amounts of soluble and protamine insulin were greater than the amount of soluble insulin required prior to protamine therapy. The increase was from 12 to 20 units daily. In 2 patients there was a gain of 10 and 20 pounds; in 2 patients there was a loss of 6 pounds; in the others, there was no change in weight. In 2 patients the tendency to insulin shock was diminished, and in 2 patients who had previously been admitted several times in diabetic ketosis there were no incidences of severe ketosis. The rest of the patients showed no significant change.

Of the entire group, only 3 patients have been adequately controlled finally on protamine alone (Cases 2, 12, 13). These 3

TABLE 3.—STATUS OF PATIENTS ON SOLUBLE AND ON PROTAMINE INSULIN.

Case No.	ON SOLUBLE INSULIN.				ON PROTAMINE INSULIN.			
	Diet in grams.		Weight changes.	Clinical condition of patient.	Diet in grams.		Weight changes.	Clinical condition of patient.
	Carb.	Prot. Fat.			Carb.	Prot. Fat.		
1	200	70	85	Constant	Admitted to hospital 7 times, either in coma or severe ketosis. Frequent insulin shocks. Very unstable.	250 70 85	Gain of 20 lbs. in 7 mos.	At start was fairly well controlled. After few mos. glycosuria became marked with occasional acetoneuria, necessitating increase in insulin requirement. No admissions to hospital.
2	250	70	85	Constant	Four admissions to hospital for varying degrees of ketosis. Also having many insulin shocks. Chronic cholecystitis.	250 70 85	Gain of 17 lbs. in yr.	Occasional mild insulin shocks; mild consistent glycosuria. No further attacks of cholecystitis. Increase in protamine insulin needed.
3	250	75	85	Constant	Subject to insulin shocks with psychotic manifestations. Never in severe ketosis. No infections.	250 75 85	Constant	Occasional mild insulin shocks. Mild consistent glycosuria. Requirement for protamine decreased; soluble insulin increased.
4	200	75	85	Unable to gain	Subject to frequent insulin reactions and periods of marked glycosuria.	200 75 85	Gain of 10 lbs.	Fairly well controlled. No ketosis. Occasional mild glycosuria. No infection. Protamine insulin decreased, soluble insulin increased for control.
5	200	75	85	Unable to gain	Subject to frequent insulin shocks. Many upper respiratory infections. Never in severe ketosis.	200 75 85	Unable to gain	Occasional mild glycosuria. Frequent insulin shocks. Required increase in protamine insulin for control.
6	250	75	85	Slow gain	Frequently in shock or mild ketosis. Many upper respiratory infections.	250 75 85	Slight gain	Did well for first few mos., then had increasing glycosuria with acetoneuria, alternating with severe shock. Protamine discontinued.
7	200	75	85	Gain of 30 lbs. in 4 yrs.	Occasional insulin shock or glycosuria. No infections.	200 75 85	Constant	Occasional mild insulin shock with occasional glycosuria. Status same as at outset.
8	200	65	85	Constant	Marked tendency to insulin shock. No infections.	200 65 85	Loss of 7 lbs. in past 6 mos.	Patient controlled at outset. Later had marked glycosuria and acetoneuria and periods of severe insulin shock.
9	250	65	85	Constant	Stable. Occasional insulin shock and short periods of glycosuria.	250 65 85	Loss of 7 lbs. in 10 mos.	Controlled adequately. Slight decrease in protamine insulin.

10	300	75	85	Slow gain	Occasional insulin shocks. Well controlled.	Well	300	80	85	Constant	Shows glycosuria. Protamine had to be discontinued and patient was returned to soluble insulin.
11	250	65	85	Constant	Pernicious anemia since 1932. Seven admissions to hospital for ketosis. Frequent glycosuria.		250	85	85	Loss of 6 lbs. in 4 mos.	Glycosuria present. No insulin shock. Soluble insulin had to be added for control.
12	350	75	85	No gain. Undernourished.	Six admissions to hospital in severe ketosis or coma. Easily thrown into shock by overactivity		350	75	85	Gain of 12 lbs. in yr.	Fairly well controlled. Moderate tendency to shock. Total units of protamine decreased. Does not require soluble insulin.
13	200	65	85	Constant	Well controlled.		200	65	85	Slow gain	Fairly well controlled. Only mild glycosuria or shock.
14	300	75	85	Unable to gain	Chronic sinusitis. Frequently in ketosis.		300	75	85	Slight gain	Chronic sinusitis unimproved. Protamine requirement increased. Moderate glycosuria.
15	200	65	85	Constant	Frequent insulin shocks. Subject to rectal abscesses recurring with ketosis.		200	65	85	Constant	Did well at onset. Diminution in shock after 9 to 10 mos. Had periods of marked glycosuria followed by prolonged insulin shocks which necessitated discontinuance of protamine insulin.
16	250	75	85	Slow gain	Numerous admissions to hospital for ketosis and infection.		250	75	85	Slow gain	Did fairly well at outset. Then had many head colds requiring increasing amounts of soluble insulin. Protamine discontinued.
17	250	75	85	Steady gain	Equal tendency to ketosis and shock. Numerous upper respiratory infections.		250	75	85	Constant	Patient observed in hospital for 2 mos. with frequent adjustments of protamine and soluble insulin unsuccessfully. Discontinued.
18	250	65	85	Slow gain. Undernourished	Two episodes of coma. Greatest tendency to insulin shock. No infection.		300	65	85	Early gain of 5 lbs.	Patient observed in hospital for over 2 mos. Unable to control successfully. Protamine discontinued.
19	295	115	150	Steady gain	Little difficulty in control.		300	80	85	Loss 10 lbs.	Observed in hospital for 1 mo. Unable to control successfully. Protamine discontinued.
20	350	80	120	Constant	Pulmonary tuberculosis with empyema. Fairly well controlled.		350	80	120	Constant	Observed in hospital for 1 mo. In spite of many adjustments unable to control successfully. Protamine discontinued.

patients have been apparently improved by the administration of protamine insulin. The improvement is evident in the following ways. The total number of doses required daily has been decreased from 4 to 2. Case 2, although still showing a mild glycosuria, has gained 17 pounds since the institution of protamine therapy. Case 12, previously subject to ketosis or shock, has had no admissions in shock, and although still showing a moderate glycosuria, feels very much improved. He has gained 12 pounds during the past year. Case 13 has gained a moderate amount of weight and has only a tendency to mild glycosuria or shock.

Discussion. There is no question in our minds that the 3 patients who are now controlled on protamine insulin alone have been definitely improved by this form of therapy. In addition, they have been spared the necessity of frequent insulin injections which is important to the patient. Of the remaining 17, we were unable successfully to transfer 4 patients from soluble to protamine insulin, and 5 were forced to discontinue protamine insulin after an adequate clinical trial of 8 months or more. Thus of the entire group, 9 patients, which is almost 50%, were unsuccessfully treated with protamine. In the remaining 8 patients it was necessary to use soluble as well as protamine insulin to control the diabetes. It seems to us that this is not a satisfactory procedure and that it is debatable whether or not these patients are any better off on this combination than they were on the soluble insulin alone.

When protamine insulin was first used in these patients there seemed to be some improvement and the number of doses of protamine insulin require daily was less than the number of doses of soluble insulin. The reason why this did not continue for more than about 6 months is problematical. One explanation that occurs to us is that repeated subcutaneous injections of protamine insulin may cause fibrosis of the underlying tissue and so interfere with uniform absorption of the protamine insulin. This is borne out by the fact that in many of the patients small nodules appear in the subcutaneous tissue after the prolonged use of protamine insulin. These are hard and firm and disappear slowly. Obviously, there must be an inconstant absorption of the protamine insulin to explain the alternating periods of glycosuria and shock which we observed in 5 of the patients. Perhaps the greatest disadvantage in the use of protamine insulin is the occurrence of insulin shock, of which the patient himself is unaware because of its insidious onset. One of the early manifestations of hypoglycemia induced by protamine insulin may be severe and intense headache which often persists for 48 hours. When protamine insulin is used, particular attention should be paid to the complaint of headache, bearing in mind that hypoglycemia may accompany it.

It is not our purpose in this report to detract from the value of an insulin preparation which can be absorbed slowly and therefore has a

definite theoretical advantage. We do feel, however, that a favorable response in the early period of protamine zinc insulin therapy does not necessarily mean that the patient will continue to be benefited. In evaluating the efficacy of protamine therapy it is necessary to observe the patients over prolonged periods and it seems to us that if improvement is not effected after a 6 months' trial, protamine insulin should be discontinued. Patients in whom protamine insulin is at first effective should be watched, after a few months, for evidences of irregular absorption and its ensuing alternating periods of severe glycosuria and hypoglycemia.

All the patients treated in this group were obviously severe diabetics, so that this was a searching test of protamine insulin. We have not attempted to substitute protamine for regular insulin when the patients required only 1 or 2 doses of insulin daily. It may be that patients requiring 2 doses daily could be reduced to 1 dose daily, in which case there would be an indication for substituting protamine for soluble insulin. Where the patient is controlled on one dose of soluble insulin daily we would doubt that there was any advantage in changing from the regular to the protamine insulin.

Summary. Twenty patients with diabetes mellitus, who had been observed for periods of 3 to 72 months on regular insulin in the diabetic clinics of this hospital, were transferred to protamine zinc insulin.

All of the patients treated were severe diabetics, 14 requiring 4 doses of soluble insulin daily and the rest 3 doses daily prior to the start of protamine zinc insulin.

It was impossible successfully to transfer 4 of the patients to protamine insulin and this form of therapy was discontinued at the end of 1 to 2 months. Of the remaining 16, after 8 months or more of protamine therapy, it was found necessary to return 5 of the patients to soluble insulin because of the occurrence of alternating periods of uncontrolled glycosuria and insulin shock. Of the remaining 11, 8 have required soluble insulin as well as protamine insulin in order to control the diabetes.

In 3 patients the diabetes was adequately controlled on protamine insulin alone. In only these 3 patients do we believe that beneficial effects followed the use of protamine insulin.

Since this paper was submitted for publication protamine insulin had to be discontinued in two more of the patients (Cases 10 and 14) because of increasing glycosuria. One additional case (No. 21) a 15-year-old girl, has been treated successfully with protamine alone for a period of 7 months making a total of 4 severe diabetics successfully treated with protamine alone. It may be of some significance that 3 of the successfully treated patients were found to have low basal metabolic rates of -15% , -20% and -22% (Cases 5, 12, and 21). It may be that lowered thyroid activity would tend

to render these patients more sensitive to the action of insulin. If this were the case, it would naturally follow that a more slowly absorbed insulin would be more effective and that less of it would be required to control the glycosuria. Possibly this may be one of the reasons for the successful response of some patients to protamine insulin.

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CHANGES IN THE GLUCOSE TOLERANCE TEST OCCURRING DURING AND AFTER INSULIN SHOCK THERAPY FOR SCHIZOPHRENIA.

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MANY papers have appeared on the glucose tolerance test in the psychoses,^{2,9,16,19-21,28} A survey of the literature has been summarized by McCowan and Quastel²¹ in their statements: "On two points there is a general agreement: (1) The fasting blood sugar level of psychotic patients is generally within normal. (2) A disordered carbohydrate metabolism (*i. e.*, a lowered tolerance) is very frequently found in psychotic patients." In addition to the frequent disturbance in the tolerance to carbohydrates as reflected by the glucose tolerance curve, they found in their work some correlation between the mood of the patient and the blood sugar content in manic depressive patients but not in schizophrenics. More recent papers have reported no such correlation, and Gildea, Mailhouse and Morris¹¹ found an increase in blood sugar in normal persons under emotional strain but not during the emotional states of patients with mental diseases.

We are reporting the data from a study of the glucose tolerance curves of 22 schizophrenic patients ranging in age from 15 to 34 years, treated with insulin shock therapy and observed for varying periods up to 10 months after treatment. We feel that these changes are sufficiently marked to justify their presentation.

The technique followed for the insulin shock treatment is that outlined by Sakel.²³ Patients were usually given the treatment 6 days a week after reaching the coma dose, which ranged between 55 and 200 units.

Three-hour glucose tolerance tests were obtained before, during and after the course of treatment. After discharge from the hospital the patients reported at intervals for repetition of the glucose tolerance test.

Blood sugars were determined by a modification of the Folin-Wu method, after 1.5 gm. of glucose per kilo of body weight were ingested. In a few cases, glucose in amounts of 100 gm. was used when the weight of the patient could not be correctly determined. It is generally accepted that such variations in the amount of glucose ingested have no important effect on the curve obtained.

Table 1 presents observations on the 22 patients studied. As far as could be determined by careful physical and laboratory studies these patients showed no evidence of clear-cut disease other than schizophrenia. The following features seem significant to us: (a) The variation from the normal glucose tolerance in the pre-treatment glucose tolerance curves; (b) the hyperglycemic (diminished tolerance) type of curve that occasionally occurred during the course of shock therapy. (c) The hypoglycemic (increased tolerance) type of curve that occurred most frequently and more particularly at long intervals after treatment had been terminated.

Before treatment, 41% of our cases showed an abnormal curve. While there appears to be no obvious explanation, diet is one important factor which we feel should be stressed when dealing with psychotic patients and particularly those undergoing insulin shock therapy. A diminished dextrose tolerance subsequent to starvation has been observed in animals by du Vigneaud and Karr¹⁰ and in humans by Himsworth¹³ and others. The investigations of Sweeney²⁷ using different diets are particularly suggestive in this work. He showed that as a diet rich in fat decreased the tolerance, so did a diet rich in carbohydrate definitely increase it. The psychotic patient, whose delusions have altered his diet, is not uncommon. Further factors to be considered in explaining altered glucose tolerance are endocrine and toxic disturbances that may not fit any definite disease pattern.^{7,8,14,24} To a lesser degree, exercise and muscular activity prior to the tolerance test affect the tolerance curves obtained.²⁶

It will be seen from Table 1 and Fig. 1 that during treatment and as long as months after the last treatment the patient frequently

TABLE 1.—GLUCOSE TOLERANCE CURVES IN 22 SCHIZOPHRENIC PATIENTS BEFORE, DURING AND AFTER INSULIN SHOCK THERAPY IN RELATION TO TREATMENT DETAILS.

Case.	Date.	Blood sugar values in milligrams per 100 cc.					Relation- ship to treatment: days after last.	No. of treat- ments to date.	Coma dose.	Effect on schizo- phrenia.
		Fast- ing.	$\frac{1}{2}$ hr.	1 hr.	2 hrs.	3 hrs.				
M. McD.	1937									
	6-15	79	84	79	70	91	Before			
	7-1	87	112	116	59	61	Before			
	8-10	100	138	148	104	94	1	24	85 U	Fair
	9-18	100	123	116	79	89	2	43	110 U	
	11-18	59	100	96	82	72	62	43		
D. M.	7-21	109	118	161	100	96	Before		Up to	Good
	9-13	107	164	177	134	91	30	15	80 U	
A. C.	9-2	59	82	109	96	96	Before			
	10-13	82	82	68	61	54	23	6	Up to	Good
	10-29	70	100	91	70	54	39	6	75 U	
E. G.	7-23	112	177	150	153	150	Before			
	8-18	87	114	104	91	59	2	12	70 U	Good
	9-23	63	94	87	77	51	37	12		
	11-18	70	65	70	68	54	91	12		
L. A.	5-17	91	256	260	200	132	Before			
	7-20	87	240	248	121	82	1	40	70 U	Good
	8-11	77	161	100	77	49	8	30		
R. B.	1-7	75	79	127	118	75	Before			Good
	2-24	77	138	153	134	63	30	18	75 U	
	11-10	89	161	200	130	68	270	18		
J. A.	1936									
	12-30	84	180	143	84	49	Before			
	1937									
	2-5	84	112	138	87	63	15	27	85 U	Good
	7-27	77	132	71	77	32	222	27		
	9-10	79	107	82	68	63	263	27		
F. B.	11-11	75	109	98	70	72	294	27		
	1-5	75	158	177	138	104	Before			Good
	2-24	75	77	87	72	62	33	9	65 U	
	10-11	75	116	96	68	63	280	9		
R. L.	10-11	87	127	136	114	91	Before			
	10-25	72	109	125	98	59	Before			
	11-20	84	125	177	145	87	1	18	145 U	Good
	12-3	75	109	116	96	63	4	24		
	12-7	54	68	100	112	70	8	24		
M. P.	8-3	91	92	121	112	82	Before			
	10-22	77	94	150	116	104	14	50	60 U	Poor
	12-14	75	94	91	89	75	77	50		
A. K.	9-14	70	189	197	143	82	Before			
	11-2	68	145	132	96	87	1	22	110 U	Poor
	12-14	68	82	114	79	42	1	55	110 U	

Case	Date.	Blood sugar values in milligrams per 100 cc.					Relation- ship to treatment: days after last.	No. of treat- ments to date.	Coma dose.	Effect on schizo- phrenia.
		Fast- ing.	1 hr.	1 hr.	2 hrs.	3 hrs.				
N. B.	6-30	94	109	116	127	132	Before			
	7-6	132	145	200	230	177	Before			
	8-25	77	79	70	63	63	10	26	90 U	Good
	8-27	61	84	82	79	56	12	26		
	9-8	65	101	82	70	59	24	26		
	11-18	68	79	63	65	79	94	26		
J. W.	6-29	98	79	98	84	84	Before			
	7-6	82	109	107	89	70	Before			
	8-20	114	164	158	130	116	1	30	200 U	Fair
	8-30	92	116	138	89	63	3	34	200 U	
	9-7	79	109	91	77	54	4	35		
	10-7	82	132	109	68	84	34	35		
	11-10	79	136	100	87	107	67	35		
C. M.	6-28	77	123	112	102	123	Before			Good*
	7-6	79	132	153	118	100	1	5	130 U	
	7-20	91	123	114	98	75	3	12		
	9-11	89	96	77	59	70	43	18		
M. N.	7-16	65	82	118	193	177	Before			Good
	9-21	77	116	94	63	68	2	26	60 U	
	10-22	65	123	82	79	72	1	51	65 U	
	12-7	63	87	84	72	72	40	51		
J. L.	8-10	65	132	134	100	82	Before			Fair
	9-16	68	125	96	72	51	1	23	105 U	
	9-22	94	130	148	94	56	1	27	105 U	
	12-4	72	84	111	102	68	43	40		
D. T.	8-25	91	138	118	87	84	Before			Poor
	9-16	68	114	132	100	91	1	3	75 U	
	11-23	76	96	125	72	68	39	16		
	10-14	70	94	109	77	87	3	16		
A. Z.	5-24	109	123	91	89	84	Before			Good*
	8-14	91	184	184	121	114	1	47	75 U	
	9-20	75	82	96	72	89	6	69	90 U	
	11-24	75	127	82	72	40	71	69		
L. P.	9-2	68	82	77	77	77	Before			Fair
	9-7	68	70	77	65	69	Before			
	10-22	59	72	75	100	72	1	28	175 U	
	12-8	54	77	65	65	59	19	49		
M. K.	9-22	77	116	134	138	100	Before			Poor
	11-24	68	118	100	97	89	1	44	115 U	
	12-10	63	87	94	116	96	1	54	120 U	
D. S.	10-21	123	136	138	114	100	Before			Good
	12-13	54	72	91	94	82	1	20	160 U	
M. S.	8-5	112	145	100	96	82	Before			Good*
	8-26	75	100	150	84	98	1	15	55 U	
	9-10	75	112	82	77	69	12	16	55 U	
	10-2	75	116	116	96	89	3	28	55 U	
	10-18	70	82	104	82	63	2	37	70 U	
	11-24	82	98	91	87	75	1	59	95 U	
	12-13	59	89	77	75	77	1	70	110 U	

* Relapse after discharge.

showed a hypoglycemic type of curve. This occurred in 73% of the cases. Three of 4 patients followed for 10 months after the termination of treatment showed this type of response to repeated tests, while 7 of 8 patients followed for 2 to 4 months still showed an increased tolerance with the curve hypoglycemic in type. It was the most consistent finding in our data. The patient, at this time, was often out of the hospital, adjusted to a different environment, not infrequently working and partaking of no special diet. The reference to diet is emphasized again because the patients during the course of therapy were given high carbohydrate diets to counteract any possibility of "after shock." This, as mentioned before,

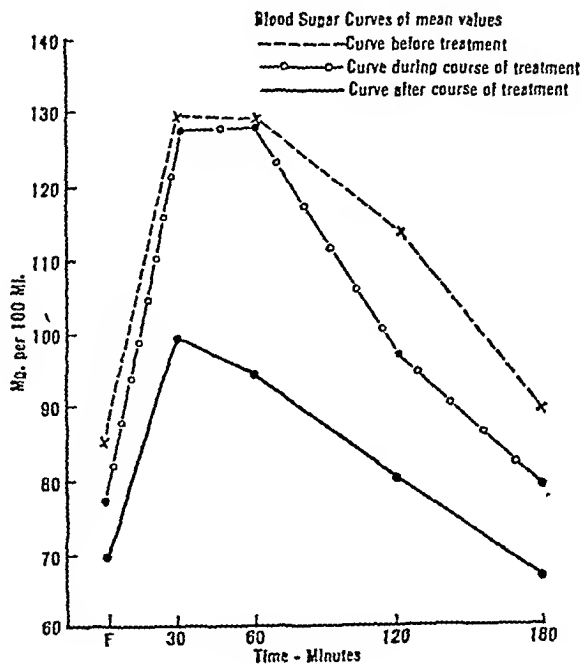


FIG. 1

might lead to the increased tolerance type of curve. We could discover but one reference to a similar finding in the literature. Müller²² in a thorough review of insulin and metrazol treatment states that he has found spontaneous hypoglycemia occurring after treatment is terminated, and gives it as one of the bits of evidence for humoral changes occurring after insulin treatment.

During the course of therapy in 4 patients, a markedly hyperglycemic type of curve was obtained. In 3 patients these curves were obtained during the day immediately following a treatment day; in 1, 30 days after the last treatment. This patient did not return for subsequent check-up. This is the type of curve that has

recently been reported by Looney and Cameron¹⁸. In 7 of the 9 cases studied by them the tolerance was measured the day after the last treatment. They suggest that the change may be due to the stimulation and sensitization of the adrenal mechanism, since it has been shown by Cannon, McIver and Bliss⁵ and Britton, Geiling and

TABLE 2.—BLOOD SUGAR RESPONSES TO 1 CC. OF ADRENALIN (1:1000) INTRAMUSCULARLY IN 16 SCHIZOPHRENIC PATIENTS.

Case.	Blood sugar values, milligrams per 100 cc.				Date, 1937.	Comparative trend of post-treatment curve.
	Fast- ing.	10 min.	30 min.	60 min.		
A. K. . . .	63	79	94	104	9-30	Increase
	77	82	87	116	12-24	
M. C. . . .	68	79	100	100	8-21	Increase
	54	70	82	104	12-22	
C. S. . . .	61	77	150	145	9-16	Decrease
	75	109	116	114	12-27	
N. B. . . .	100	104	132	200	7-7	Decrease
	79	134	123	77	8-26	
P. G. . . .	84	82	89	112	8-2	Decrease
	75	87	96	100	8-20	
M. H. . . .	77	77	132	121	10-8	Increase
	72	75	141	132	11-20	
R. L. . . .	65	84	100	125	9-25	Increase
	70	87	123	143	11-30	
C. M. . . .	84	87	134	180	6-28	Decrease
	89	107	145	109	7-21	
D. M. . . .	84	89	112	132	7-23	Decrease
	65	75	89	98	9-18	
M. McD. . .	87	82	82	107	6-28	Decrease
	91	96	87	91	8-18	
	68	72	123	116	9-27	
S. P. . . .	70	89	96	164	4-15	Decrease
	77	100	102	125	5-26	
	84	94	114	118	7-23	
C. R. . . .	75	94	134	177	7-28	Increase
	75	109	107	141	8-25	
J. W. . . .	65	82	89	82	7-10	Increase
	79	79	82	87	9-15	
	63	77	116	130	9-18	
L. A. . . .	91	109	150	161	5-22	Decrease
	77	91	124	77	8-10	
D. T. . . .	72	84	87	96	8-27	Increase
	54	87	91	114	12-21	
J. L. . . .	72	79	96	145	8-7	Increase
	70	116	134	200	12-18	

Calvery⁴ that hyperadrenalinemia occurs after insulin shock. The duration of this state, however, after the insulin shock has been remedied does not seem to have been determined. It is possible that hyperadrenalinemia may persist for days and thus explain these findings. It must be recalled that previous insulin administration has been shown to cause a temporary loss of tolerance for carbohydrates in normal individuals. The duration of this effect is said to be 2 to 3 days.^{1,6,29} However, the glucose tolerance curves obtained long after treatment had been terminated are of a different type and are not satisfactorily explained by this hypothesis.

Soskin, Allweiss and Cohn²⁵ maintain that it is the liver and not the pancreas which is the most potent factor in determining the nature of the dextrose tolerance curve. They state, "Results show that there is no appreciable store of insulin in the tissues by which the dextrose may be affected once the pancreas is removed. . . . It is obvious that although the liver is a major factor in determining the dextrose tolerance curve, it can respond normally to sugar administration only when under the influence of a suitable endocrine balance."

That liver insufficiency, if present, is not pronounced, is suggested by normal results of bromsulphalein tests, by absence of a significant change in serum albumin or globulin and by normal cholesterol—cholesterol ester ratios.

Following a course of therapy we have found a definite tendency toward lower basal metabolic rate (calculated from oxygen consumption) in the majority of our patients. Again, diet may be a factor in explaining this change, since diets given during the course of treatment were far richer in carbohydrates than those before treatment. This change in diet may alter the respiratory quotient sufficiently to influence basal metabolic rate calculations. Although increased glucose tolerance is the usual finding in hypothyroidism and hypopituitarism, these patients did not show any of the obvious signs of the hypo-function of these glands. However, the possibility that depression of pituitary function may occur is one that we are pursuing with further studies. In this connection, the recent work of Long,¹⁷ on the control of adrenals through the pituitary, is significant. Increased pancreatic activity with hypersecretion of insulin is not a plausible explanation since it is accepted that administration of a hormone leads to diminished endogenous secretion of that hormone and not to increased hormonal production.

That hypoglycemic sugar tolerance curves in response to insulin shock therapy are not peculiar to schizophrenia is suggested by the studies on a small group of patients with manic depressive (depressed) psychoses and a case of dementia paralytica. In all of these cases a hypoglycemic type of response was obtained after treatment.

Finally, the glycemic response to adrenalin was determined before

and after a course of therapy on a series of patients. One cubic centimeter of 1:1000 adrenalin was given intramuscularly to the fasting patients. Blood sugar determinations were made before injections and 10 minutes, 30 minutes and 1 hour after injection. (Blood pressure and pulse reading were obtained at 5-minute intervals.) This test was formulated in an attempt to determine possible diagnostic changes in the response of the adrenal-sympathetic system as a result of prolonged administration of insulin^{12,15} and also as a possible indicator of liver function.³ While the majority of curves "after-treatment" show a continuous rise of blood sugars which may be higher than those in the "pre-treatment" curves (Table 2), the findings on the whole do not offer convincing evidence for a sensitization of the adrenal-sympathetic mechanism.

We believe that the tendency toward spontaneous hypoglycemia is probably reflected in the increased appetite, resulting in marked progressive weight gain seen in these patients months after the treatment has been terminated. It may also explain the atypical hypomanic reactions that occur infrequently after treatment in some of these patients. However, it does not seem to be related to the possible therapeutic outcome of the disease. The similar type of response shown by the other forms of mental disease suggests that this form of therapy does not owe its effect to an influence upon a fundamental endocrine disturbance peculiar to schizophrenia.

Summary and Conclusions. 1. The glucose tolerance curve is abnormal in a relatively high percentage of our cases of schizophrenia. This is in agreement with the findings of most of the workers in the field.

2. During and following the course of insulin shock therapy we have noted definite changes in the character of the glucose tolerance curve. A biphasic variation in the type of curve is suggested. During a course of treatment, particularly immediately after a course of treatment has been terminated, a hyperglycemic (diminished tolerance) type of curve is at times obtained. However, in many patients immediately, and in most, many days and months after the treatment has been terminated, a hypoglycemic (increased tolerance) curve prevails. Ten of 12 patients followed from 2 to 10 months after their last treatment showed this type of response.

3. These findings are probably not peculiar to schizophrenia in its therapeutic response to insulin therapy, nor are they of prognostic value.

These cases are reported through the courtesy of the Psychiatric Staff of the Philadelphia General Hospital.

Grateful appreciation is hereby extended to Eli Lilly and Company who furnished the insulin for this work.

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THE EFFECT OF BENZEDRINE ON CILIARY MOVEMENT.

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IN a previous communication,² benzedrine (benzyl-methyl-carbinamine) was administered as an inhalant and was found to relieve nasal congestion in patients afflicted with coryza but not to affect the duration of the cold. At the same time, a 0.1% aqueous solution of the sulphate of benzedrine was found to decrease the movements of cilia in the mucosa lining the pharynx and esophagus of frogs. The object of the present further investigation was to ascertain if the free base of benzedrine, which was that form used by inhalation in the former work,² had an effect on cilia similar to that of the sulphate of benzedrine which was the substance whose effect on cilia was studied and reported at that time.

Some otolaryngologists are—and some are not—concerned about the possible harmful effects to the mucous membrane of the nose and throat of repeated use of recently proposed preparations containing vasoconstrictor drugs such as epinephrine, ephedrine, benzedrine or meta-synephrine in the local treatment of coryza. By local vasoconstriction, these preparations give to the patient an immediate pleasing relief from “stiffness of the head.” The effect wears off after some minutes or at most in an hour or two and the patient again applies the remedy. The cold runs its usual course but the patient is free of the distressing and exasperating symptoms of nasal turgescence. It is reasonable to ask, therefore, whether the harmful effects of these substances on mucous surfaces, which are probably slight from *single* applications, should be neglected in view

of the immense relief experienced by the patient. Apropos of this question, it may be recalled that the recognized treatment of many surface lesions involves application of substances which are known to destroy or harm tissue.

There is a further possible factor to be considered. Some believe that the congestion of the nasal mucosa is Nature's method of combating colds by asphyxiating the virus of coryza through inhibiting or preventing the passage of air through the nasal cavity.³ Should this theory be true, then the nasal passage presumably should not be opened by vasoconstrictors. The situation may prove to be analogous to the relation between antipyretics and fever, antipyretic drugs having considerably less use now than formerly.

TABLE 1.—THE EFFECT OF TOPICAL APPLICATION OF SEVERAL SYMPATHOMIMETIC SUBSTANCES UPON CILIARY MOTION OF THE ESOPHAGEAL MUCOSA OF FROGS.

Substance.	Concentration, %.	Average percentage depression of ciliary motion after:			Percentage of experiments showing depression.
		1 min.	2 mins.	3 mins.	
Benzedrine	0.05	38	44	44	92
Benzedrine sulphate . . .	0.05	32	36	36	83
Benzedrine	0.1	46	48	52	92
Benzedrine sulphate . . .	0.1	38	42	47	92
Meta-synephrine hydro- chloride	0.1	17	23	25	75
Ephedrine hydrochloride .	0.1	25	25	32	88

Method. The procedure used in this further experimental study of benzedrine was identical to that previously reported.² The effect of a number of related drugs on ciliary motion was evaluated by comparing the rate at which cilia lining the esophagus of the frog carried a light object a given distance before and after application of a solution of the drug. To facilitate interpretation of results, a slightly different method has been used to summarize them. The average passage time of not less than 24 and not more than 32 experiments was calculated before applying a solution to be tested and after the end of 1, 2 and 3 minutes after applying the solution. The initial average was then subtracted from the average at the end of 1 minute, this difference was divided by the average at the end of 1 minute and multiplied by 100 to give the percentage change in the rate of ciliary motion. Corresponding percentage changes were calculated at the end of 2 and of 3 minutes. These mean percentage changes have been assembled in Table 1. To show the regularity with which ciliary motion was depressed by all of the solutions studied, the number of experiments in which depression was obtained was calculated as a percentage of the total number of experiments and these latter figures are listed in the last column of Table 1.

After the third reading had been obtained, the mucosa was washed with saline and further passage times recorded. In the majority of instances, the cilia recovered from the depressant effects of the solutions applied, though recovery was seldom complete. This observation, however, formed the basis of the previously made statement that a *single* application of these sympathomimetic compounds probably has little permanent effect upon ciliary movement.

Results. Six solutions were tested and in the concentrations noted in Table 1. In comparable concentration, meta-synephrine

or neo-synephrin was found to have the least depressant effect, confirming an earlier report.¹ Ephedrine hydrochloride averaged 25 to 50% more toxic in this respect than meta-synephrine. Benzedrine sulphate was correspondingly 80 to 120% more toxic and the free base of benzedrine, which was that form used as an inhalant in our previous work,² was 100 to 170% more toxic on the average. Both in a concentration of 0.05 and 0.1%, benzedrine was found more toxic than benzedrine sulphate. A part and possibly a large part of this increased toxicity of the free base of benzedrine may undoubtedly have been due to the fact that a given percentage solution of the free base contains more benzedrine than the same concentration of benzedrine sulphate, the molecular weight of the latter substance being greater than that of the former.

Conclusion. In concentration of 0.05 and 0.1% in distilled water, the following sympathomimetic compounds were found depressant towards ciliary movements of the esophageal mucosa of frogs and in the following order of decreasing toxicity: benzedrine, benzedrine sulphate, ephedrine hydrochloride and meta-synephrine or neo-synephrin hydrochloride.

Substances used in this work were generously provided as follows: benzedrine and benzedrine sulphate by the Smith, Kline and French Laboratories; ephedrine hydrochloride by the Abbott Laboratories; neo-synephrin hydrochloride by Frederick Stearns & Co.

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THE ANTIDOTAL ACTION OF PICROTOXIN IN ACUTE INTOXICATION BY THE BARBITURATES.

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THERE are accumulated sufficient experimental data to establish picrotoxin as an active antidote for acute poisoning from derivatives of barbituric acid. In sublethal doses of these compounds, picrotoxin shortens the recovery time; in lethal doses, within certain limits, it prevents death; and, when hopelessly large doses have been given, it prolongs the life of laboratory animals.^{1, 6, 7, 8}

Recent controlled clinical studies² and case reports^{3-6, 9} have established picrotoxin as an effective physiologic antidote for barbituric acid intoxication in humans.

Four case reports are herein presented as examples of the clinical effectiveness of picrotoxin,* and to outline briefly the therapeutic procedures found most efficacious.

* The picrotoxin used in these studies was supplied through the courtesy of the Abbott Laboratories, Inc.

Cases reported are those in which the drug and amount taken could be established with reasonable accuracy.

Case Reports. **CASE 1.**—A white female, aged 24, swallowed 114 gr. of sodium amytal. Twelve hours later a hotel physician treated the patient. A gastric lavage was done, strychnine gr. 1/40 and coramine 3 (2 cc.) ampules were given intramuscularly. The patient was brought to the hospital soon thereafter since the physician believed pulmonary edema was developing.

Examination on Admission. The patient was in coma with completely relaxed, flaccid musculature. There was no reaction to painful stimuli. Superficial and deep reflexes were absent. The pupils were 3 mm. in diameter and did not react to light. The skin was cyanotic, hot and dry. Rectal temperature was 102° F. The airway was obstructed, mucus was profuse in the pharynx and signs of pulmonary edema were present. Respirations were shallow, the rate 36 to 40 per minute. Pulse rate, 120; blood pressure, 110/60.

Treatment and Course. A tube was introduced into the stomach and a thorough lavage with a solution of sodium bicarbonate was done. A spinal puncture was done and the patient was catheterized. A soft rubber endotracheal airway was placed translingually and the lower respiratory tract cleared of mucus by suction. An intravenous infusion of 5% glucose in normal saline was instituted. Picrotoxin was given in 3 mg. doses by way of the infusion tube at irregular intervals. From 10 A.M. to 7 P.M. 129 mg. were administered. The early doses resulted in deeper respirations only. The later doses were followed by twitching of the facial muscles. Shortly after 7 P.M., the patient moved her head and legs. She slept throughout the night but could be stimulated to open the eyes and move the head or extremities. At 7 P.M., the patient was reacting on the endotracheal airway. It was removed and the patient moved her body. At 1 P.M. there was verbal response to questions and the patient complained of a sore throat and numbness in both hands. Convalescence was uneventful thereafter. The patient was discharged on the fourth hospital day. At discharge, there was a bilateral ulnar palsy.

CASE 2.—A white female, aged 28, 8 hours prior to admission had taken 90 gr. of sodium pentobarbital together with some lemon extract and gin.

Examination on Admission. Patient was in coma and did not react to painful stimuli. The superficial reflexes were absent, the deep reflexes sluggish. Eyeballs were fixed centrally, pupils 2 mm. in diameter did not react to light. The respirations were shallow at a rate of 30 per minute. The airway was obstructed with mucus and from edema of the vocal cords. There were moist râles throughout the chest. Rectal temperature, 99° F.; pulse rate, 140; blood pressure, 110/80.

Treatment. Catheterized, gastric lavage, and intravenous infusion with 5% glucose in normal saline started. A soft rubber endotracheal airway was put in place and the respiratory tract cleared by suction. Forty-eight mg. of picrotoxin were given intravenously during the next hour. Respirations were stimulated, there were twitchings about the mouth followed by retching and vomiting. Patient slept throughout the day and night. The following morning was aroused and found to be rational. Recovery was complete on the third day when she was discharged.

CASE 3. White female, aged 45. Two years previous to present hospital admission had thyroidectomy for advanced Graves' disease. For past 4 months had acted strangely, drinking large amounts of alcohol and taking luminal. On the day of admission fell on the street unconscious and was taken home. At midnight was brought to the hospital. She had received 15 gr. of caffeine sodium benzoate and on admission was given 1.5 cc.

coramine intravenously. She had taken at one time (noon) 75 gr. of sodium luminal.

Examination on Admission, 1.30 A.M. Patient in coma with no response to painful stimuli. There was a thick, mucoid froth in mouth and coarse râles throughout the chest. The skin was warm, cyanotic and perspiring, the pupils were equal, regular and reacted to light and accommodation. Respirations were rapid and stertorous. Deep reflexes were absent. Pulse rate was 140, the rectal temperature 100° F.

Treatment. Patient was catheterized and the stomach lavaged. An intravenous infusion of 5% glucose in normal saline was started. Oxygen therapy by oropharyngeal insufflation, 6 liters per minute, was instituted. An active laryngeal reflex hindered using an endotracheal catheter. Picrotoxin, 1 mg. per minute, was given by way of the infusion tube, beginning at 2.30 P.M., until 15 mg. were given. This amount caused the eyeballs to oscillate, the patient to react to painful stimuli and within 5 minutes to talk incoherently. Infusion was discontinued. At 7 A.M. the patient was again in deep coma. Infusion was started and 30 mg. of picrotoxin were given intravenously during the next 30 minutes. The patient reacted to pain and began moaning. Gastric lavage was done and calomel, 1 gr. in 10 cc. water, was left in stomach. Mercupurin (1 cc.) was given intramuscularly. At 10.15 A.M. patient was in deep sleep. Eight mg. picrotoxin given intravenously caused muscle twitchings. Then 3 mg. doses of picrotoxin were given intramuscularly every 10 to 30 minutes. At 7 P.M. patient could be aroused easily and responded to spoken questions. No treatment was attempted during the night. The following morning the patient was stuporous but moved the arms and legs. An additional 3 mg. of picrotoxin were given intramuscularly. This completed a total of 122 mg. given during treatment. At 11 A.M. the patient was alert. The following day (4th) she was transferred to the Psychopathic Service where a diagnosis of involutional melancholia with suicidal tendencies was made.

CASE 4.—A white male, aged 57, attempted suicide by taking 500 gr. of sodium barbital (veronal) by mouth during the late afternoon. He was admitted to the hospital at 1.00 A.M., having received no treatment except $\frac{1}{2}$ gr. of strychnine.

Examination on Admission. An obese male in coma with flaccid, relaxed muscles did not react to painful stimuli. Reflexes were absent. The pupils dilated, centrally fixed and non-reactive to light. Respirations were 16 per minute. There were no chest râles and little mucus. The pulse rate was 100; blood pressure, 100/60; temperature, 98° F. (rectal).

Treatment. Gastric lavage and lumbar puncture done. The spinal fluid was clear and without increased pressure. An indwelling urethral catheter was inserted. A soft rubber endotracheal airway was put in place. An intravenous infusion of 5% glucose in normal saline was started. Picrotoxin, 23 mg., was given by the infusion tube at the rate of 1 mg. per minute. There was an increase in respiration and slight twitching about the eyes and mouth. The patient soon returned to the previous state, and an additional 24 mg. of picrotoxin were given at the same rate. At 8 A.M. deep coma was again evident and 21 mg. of picrotoxin were given. At 10 A.M. 39 mg., given 1 mg. per minute were required to elicit twitching about the mouth. At noon 12 additional mg. of picrotoxin produced slight tremors. By 8 P.M., the patient was again in deep coma. Picrotoxin was given at intervals throughout the night and next day. A very slow infusion was continued, gastric lavage was done at frequent intervals and sodium bicarbonate solution left in the stomach each time. On the third day, 9 to 9.30 A.M., 24 mg. of picrotoxin were given. The patient then responded to painful stimuli, opened his eyes and reacted on the endotracheal tube. Following this it was possible to arouse the patient with intravenous picrotoxin but

after an hour or more he would return to the comatose state. Then intramuscular injections of picrotoxin were given in an attempt to maintain the patient so that he would react to painful stimuli. This required about 20 mg. per hour. This schedule was continued for 20 hours and the patient was definitely more active. The endotracheal airway was removed and replaced often during the 4th and 5th days. During the next day the airway was not used, some fluids were given by mouth and the infusion was discontinued. Intramuscular picrotoxin was decreased to 10 mg. per hour. Late that day (6th) the patient responded to spoken questions but was very stuporous. During the late evening, it was again impossible to arouse the patient. He was given 42 mg. of picrotoxin intravenously within 2 hours and then became more alert than at any previous time. He answered questions readily. Intramuscular picrotoxin was resumed at 12 mg. per hour. The following morning (7th day) the patient talked clearly, took fluids by mouth and moved his arms and legs at will. Mercupurin was given to increase urinary output. Picrotoxin was discontinued. By noon he was again in a somnolent state, difficult to arouse. Intramuscular picrotoxin (20 mg. per hour) did not produce the effect it had previously. Late in the day it was necessary to give intravenously 30 mg. of picrotoxin to arouse the patient. He then talked easily, and took nourishment. He was engaged in conversation for nearly an hour and told of his schooling, war experiences and troubles. He received no picrotoxin during the night. At 7 A.M., it was impossible to arouse him. He was given 30 mg. of picrotoxin intravenously in 30 minutes' time; this produced a generalized convulsion lasting several minutes. The convulsion was finally controlled by giving 7 gr. of sodium amytal intravenously. Soon thereafter, 27 mg. of picrotoxin were given by vein and the patient responded sluggishly. He appeared very weak, although he could be aroused. Thereafter, he gradually became weaker, circulatory depression was evident, respirations slowed and became shallow. He expired on the 8th hospital day. A total of 2134 mg. of picrotoxin was given. There was 10.2 mg. of barbiturate in 20 cc. of urine collected shortly before death.

Autopsy, which unfortunately did not include the brain, revealed acute hepatitis and hypostatic pneumonia. The liver (500 gm.) contained 27.8 mg. of barbiturate and traces of picrotoxin.

Discussion and Summary.—The physical signs and symptoms in each case reported indicated severe poisoning from barbiturates. The amount of drug taken was in each case well within the range considered fatal. The patient who did not recover had received an amount that is usually regarded as hopelessly fatal. The experience with these patients suggest that in human beings, results with picrotoxin in barbiturate poisoning may be anticipated which are identical with those found by Tatum⁸ and his co-workers in laboratory animals.

In the management of patients with severe barbiturate intoxication, too much emphasis cannot be given to the therapeutic procedures in addition to picrotoxin therapy. Active, close supervision is essential. Frequent changes in position; maintenance of body temperature; support of circulation and nutrition with intravenous fluids; frequent gastric lavage and feeding; frequent catheterization; diuretics; blood transfusion; oxygen therapy and the use of an endotracheal airway; frequent cleaning of trachea by suction through the airway are indicated and their importance is not surpassed by the use of picrotoxin.

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PROTHROMBIN DEFICIENCY AND THE BLEEDING TENDENCY IN OBSTRUCTIVE JAUNDICE AND IN BILIARY FISTULA.

EFFECT OF FEEDING BILE AND ALFALFA (VITAMIN K).*

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It is well known that a bleeding tendency often develops in patients suffering from chronic biliary obstruction. Epistaxis and bleeding from gums and other mucous surfaces are of common occurrence. The surgeon frequently encounters persistent bleeding at the operating table, or from the wound afterwards. Such hemorrhage often is difficult to control, even with repeated transfusions. As a rule, the coagulation time is found to be but little in excess of normal. The bleeding time is often moderately prolonged, especially if determined by the method of Ivy.⁷ Many views have been held regarding the nature of the disturbance. Almost every clotting factor has been said by one writer or another to deviate from normal. Antithrombin has been thought by some to be excessive. One of the more popular views has been that a disturbance in calcium metabolism is responsible for the bleeding; however, calcium therapy has not been found to be particularly effective. Quick, Stanley-Brown, and Bancroft¹⁰ found that tissue juice accelerates the clotting of normal plasma more than in the case of jaundiced plasma, and they suggested that the jaundiced plasma is deficient in prothrombin.

* Aided by a grant from The Committee on Scientific Research of The American Medical Association, and more recently by a grant from The John and Mary R. Markle Foundation.

Their proof is incomplete, however. A recent review by Ravdin and Johnston¹¹ leaves the cause of bleeding in these cases an open question. Very recently considerable speculation concerning the possible rôle of vitamin K has been stimulated by the work on "hemorrhagic chick disease."

Much of the present confusion regarding the bleeding tendency in obstructive jaundice is due to lack of quantitative analysis. We have given particular attention to the development of technique for the titration of prothrombin. We have finally succeeded in developing a method^{12,13} which is independent of variables inherent in other methods. With the aid of this technique we have studied the plasma prothrombin in a number of cases of biliary tract disease, some of which had a definite tendency to bleed. We have also been able to follow the prothrombin levels during recovery and to study the effect on the prothrombin level of feeding bile, and alfalfa extract rich in vitamin K.

Methods. The prothrombin method used has been previously described.^{13,12}

The alfalfa extract used to supplement bile feeding was prepared from dry alfalfa meal (sun-cured). The solvent used in making the extract was a special lead-free, low-boiling petroleum ether known commercially as "Skellysolve A." The dry alfalfa meal was placed in flasks and extracted in series, after which the solution was filtered and concentrated by distillation. Prior to use, this concentrate was evaporated to dryness (a thick greenish greasy residue), and emulsified in human bile or in 2% bile salt (sodium taurocholate). This preparation was given by mouth in the early evening hours in doses corresponding to 200 to 400 gm. of the alfalfa meal per day. Samples of the extract were tested for their curative effect in "hemorrhagic chick disease" and found to be highly potent.

Plasma Prothrombin Level and Bleeding Tendency in Obstructive Jaundice. Table 1 shows the plasma prothrombin levels in 27 cases of obstructive jaundice. In most cases, the level was definitely below normal. However, the amount of lowering is not clearly dependent upon the intensity or duration of the jaundice.

In this series, 6 showed a definite bleeding tendency. This tendency in every instance was associated with a marked decrease in the prothrombin level, usually to less than 35% of normal. Later determinations in the cases which recovered showed that cessation of bleeding was associated with an increase in the prothrombin values.

A few cases develop very low prothrombin values and yet escape actual bleeding. In Patient 26, for example, no hemorrhage occurred, although the prothrombin fell to 37% of normal. Also, in Patient 25 there was no bleeding even though the prothrombin level fell to 20% 11 days after operation. Such cases are, however, definitely in the danger zone and serious bleeding is to be feared, especially if any operative procedure is anticipated. In several of the cases in which extensive bleeding occurred, the bleeding

tendency did not become manifest until the time of operation or shortly thereafter.

TABLE 1.—PROTHROMBIN LEVEL IN OBSTRUCTIVE JAUNDICE.

Case.	Cause of obstruction.	Serum bili- rubin, mg. %.	Dura- tion of jaun- dice.	Pro- throm- bin, %.	Bleeding tendency.
1	Carcinoma of pancreas	23	4 mos.	37	Excessive bleeding, para- centesis wound
2	Common duct stone†	5	1 mo.	60	None
3	Cholangiitis; abscess, head of pancreas*	4.6	?	23	Epistaxis; profuse bleed- ing at operation
4	Cholelithiasis*	9.8	4 mos.	69	None
5	Common duct stone†	12	?	71	None
6	Carcinoma, head of pancreas	31	3 wks.	49	None
7	Chronic cholangiitis(?)*	24	7 wks.	62	None
8	Carcinoma of pancreas; com- mon duct stone*	18	1 mo.	84	None
9	Common duct stones†	14	1 wk.	57	None
10	Common duct stone*	6	2 mos.	80	None
11	Common duct stone*	8.4	6 mos.	79	None
12	Common duct stone*	3.2	5 days	91	None
13	Common duct stone(?)	5	2 wks.	77	None
14	Cholelithiasis*	†	?	89	None
15	Common duct stone(?)†	8.4	5 wks.	64	None
16	Cholelithiasis*	21	4 wks.	84	None
17	Common duct stones†	18	?	70	None
18	Common duct stone(?)*	6.8	5 mos.	52	None
19	Carcinoma, ampulla of Vater*	29	4 wks.	66	None
20	Carcinoma of pancreas	10	3 wks.	60	None
21	Cholangiitis(?)*	21	2 mos.	34	Bruised easily; bled from gums
22	Carcinoma of pancreas†	34	4 wks.	17	Bled excessively from operative wound
23	Common duct stones*	..	6 wks.	16	Bled markedly from op- erative wound
24	Carcinoma of biliary tract*	23	8 wks.	10	Bled markedly from op- erative wound
25	Common duct stone*	11	1 wk.	51	None
26	Common duct stone(?)	29	4 wks.	37	None
27	Common duct stone*	17	6 wks.	50	None

* Denotes operative diagnosis. † Denotes autopsy diagnosis. ‡ Icterus index, 43.

Biliary Fistula: Prothrombin Level and Bile Feeding. Patients having chronic biliary fistulæ, even though there is no jaundice, at times develop a tendency to bleed similar to that seen in cases of obstructive jaundice. We have recently had the opportunity of following the prothrombin level in such a case and of studying the effect of bile feeding on the plasma prothrombin.

Case Abstract. A white woman, aged 66, had a biliary fistula of 4 months' duration. The fistula had developed following the removal of an acutely inflamed gall bladder. During this entire period the stools were acholic. On admission to this hospital there was slight jaundice. For 3 weeks pre-operatively about one-half of the bile which drained from the

fistula was given back by mouth. During this time the prothrombin varied between 58 and 45%. At operation, February 12, 1937, reconstruction of the stenosed common duct was found to be impossible and the fistula was enlarged for better drainage. Following this operation there was a farther decrease in prothrombin to 27% and there was bleeding from the wound on the 4th and 5th postoperative days. This was controlled by a transfusion. Starting on the 12th postoperative day and continuing for 6 weeks, about 400 cc. bile per day were given by mouth. This represented two-thirds of the bile which drained from the fistula. The patient steadily improved and was discharged at the end of 7 weeks.

The plasma prothrombin response to bile feeding is shown in Chart 1. The prothrombin gradually rose to a nearly normal level over a period of 6 weeks.

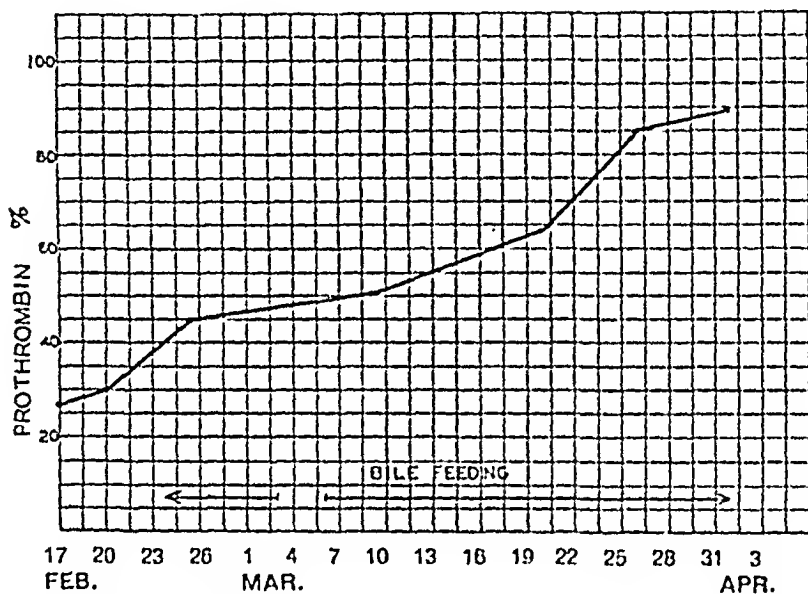


CHART 1.—Biliary fistula. Prothrombin response to bile feeding.

Effect of Bile and Alfalfa Extract Feeding on the Prothrombin Level in Obstructive Jaundice. We have studied the effect of feeding bile or bile salts supplemented with a fat soluble extract of alfalfa on the prothrombin level in a number of cases of obstructive jaundice with hypoprothrombinemia. Four of these cases are shown in Chart 2.

Case Abstracts. CASE 21.—A white woman, aged 48, had painless jaundice with acholic stools for 2 months. During the week before admission here, she bruised easily and bled from the gums at times. The day after admission, March 21, 1937, the van den Bergh test showed 22 mg. bilirubin and Duke's bleeding time was 14 minutes. On March 25 and March 31, blood transfusions of 500 cc. were given and from March 29 to March 31, 200 to 300 cc. bile were fed daily. The bleeding tendency persisted, however. During this time the plasma prothrombin was at a low level. It rapidly increased to a nearly normal level with addition of alfalfa extract (equivalent 400 gm. alfalfa meal emulsified in 100 cc. human bile daily), as shown in Chart 2. No further bleeding occurred. At operation, April 7, the obstruction, apparently high in the liver hilus, could not be relieved, and the jaundice was still present at the time of discharge, April 23.

CASE 25.—An obese white woman, aged 52, had had attacks of right upper abdominal pain with radiation to the back for the past 10 years. The attacks increased in severity and frequency during the past 3 months, and she was intolerant of fatty foods. On April 1, 1937, jaundice and acholic stools were first noted. On April 6, van den Bergh test showed 11 mg. serum bilirubin. Because of a subnormal plasma prothrombin level, she was given alfalfa extract for a 5-day period (400 gm. equivalent daily, emulsified in 100 cc. human bile for first 3 days, in 30 cc. 2% sodium taurocholate for last 2 days). The plasma prothrombin rapidly increased to a normal level (Chart 2). The jaundice persisted and, on April 15, there were 15 mg. % bilirubin. At operation, on April 17, a stone was found obstructing the common duct. The gall bladder was removed and the common duct drained. During the first 10 days postoperatively 2680 cc. bile drained from the common duct, and no bile was fed. The prothrombin fell

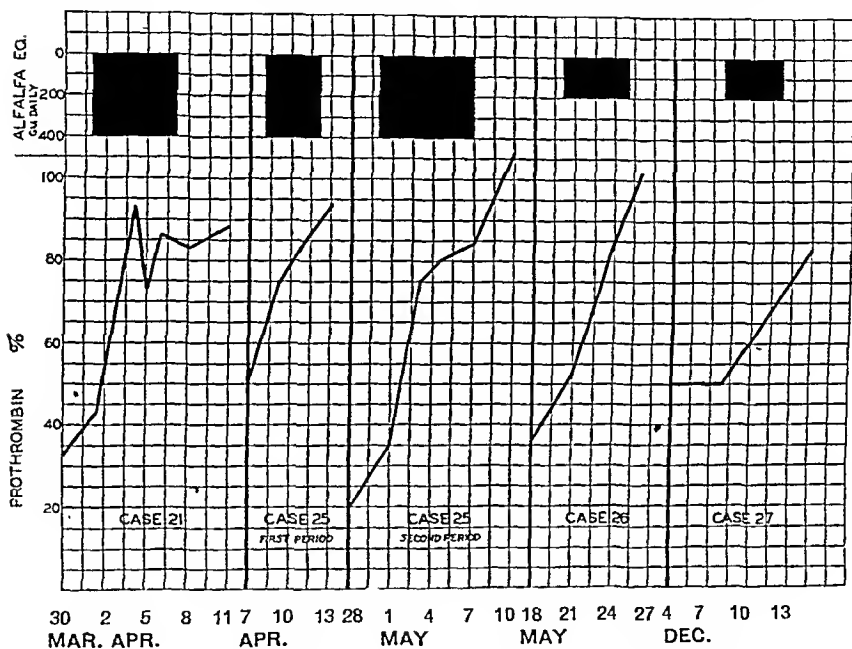


CHART 2.—Obstructive jaundice. Prothrombin response to alfalfa therapy.

gradually and at the end of this period it was 20% of normal. No spontaneous bleeding occurred, however, and the clotting time and Duke's bleeding time were not prolonged. Serum bilirubin on April 27 was 7.1 mg. Alfalfa extract, emulsified in sodium taurocholate solution, was then given, again with a rapid rise of the plasma prothrombin (Chart 2). Bile (200 to 400 cc. daily) continued to drain from the common duct; most of it was given back by mouth. During the last 18 days in the hospital, the prothrombin remained within normal limits and the jaundice subsided completely.

CASE 26.—A white woman, aged 39, gave an indefinite history of epigastric distress and pain under the right costal margin for the past 6 years. During the past month a gradually increasing jaundice with acholic stools developed. On May 18, 1937, the van den Bergh test showed 29 mg. bilirubin. No bleeding tendency was present, although the prothrombin was at a rather low level. The prothrombin rapidly rose to a normal level

during a 6-day period of feeding alfalfa extract (equivalent of 200 gm. alfalfa meal in 30 cc. 2% sodium taurocholate daily), as shown in Chart 2. During this period of therapy the jaundice persisted, with 36 mg. serum bilirubin on May 22, and 24 mg. on May 24. During the following week there was partial spontaneous relief from the biliary obstruction, and no operative procedures were carried out.

CASE 27.—A white woman, aged 27, had a severe attack of right upper abdominal pain 3 months ago. This was followed by dull pain which has persisted. Jaundice with acholic stools first was noted 6 weeks ago; this has also persisted. Van den Bergh test showed 17 mg. serum bilirubin on December 8, 1937. Clotting time and Duke's bleeding time were not prolonged. However, the plasma prothrombin was low. It was rapidly restored to a nearly normal level after feeding alfalfa extract (200 gm. equivalent alfalfa meal emulsified in 30 cc. 2% sodium taurocholate), as shown in Chart 2. At the end of this time, on December 11, there were 14 mg. serum bilirubin. The prothrombin remained at this high level throughout the patient's hospital course. Operation on December 22 revealed a stone, 2 cm. in diameter, in the ampulla, and several smaller stones in the common duct. The gall bladder was removed and the common duct drained.

The rapid rise in prothrombin obtained with bile and alfalfa feeding is quite in contrast to the very gradual rise seen with simple bile feeding in the biliary fistula case. It is to be noted that in Case 25 and Case 26 the prothrombin rose rapidly during periods of increasing jaundice. This indicates that the jaundice itself is not the essential factor in these cases.

We have had 2 patients with low prothrombin values which did not respond to alfalfa therapy. Both patients were deeply jaundiced, and in addition had evidence of extensive liver damage. Clinical impressions were a biliary cirrhosis of 3 years' duration in one case and a far-advanced malignancy involving liver in the other. The failure of these 2 cases to respond suggests that in addition to certain dietary essentials, a liver of good functional capacity is needed for the manufacture of prothrombin.

Comments. The data presented indicate that the bleeding tendency often seen in cases of obstructive jaundice and biliary fistula is due to a prothrombin deficit. Some patients fall within the danger zone and yet escape actual bleeding. Other factors, such as trauma, infection, operative hemorrhage, and exudate formation, are no doubt important in inciting actual hemorrhage. For this reason patients somewhat above the bleeding level must be considered as potential bleeders.

No doubt a variable degree of depression of liver function incident to obstructive jaundice is in part responsible for the lowering of the plasma prothrombin. We have shown^{12,13} that toxic injury of the liver produces a profound fall in the prothrombin level. Liver injury probably is important in the very rapid fall in prothrombin seen in some cases of obstructive jaundice. The biliary fistula case cited, however, indicates that the absence of bile in the intestine is of major importance. This is in accord with the recent work of

Hawkins and Brinkhous,⁶ in which they found that hypoprothrombinemia with a resultant bleeding tendency develops in dogs with chronic biliary fistula. In their experiments bile feeding prevented the fall in prothrombin. One might assume that the prothrombin deficit is due to difficulty in absorbing fat-soluble vitamins when bile is excluded from the gut. One could assume either that one of these vitamins serves as a building stone of prothrombin or that it was necessary to maintain normal function of the liver for the manufacture of prothrombin. McNealy, Shapiro, and Melnick⁸ have presented clinical evidence that the bleeding tendency in obstructive jaundice is relieved by administration of viosterol along with bile salts. No prothrombin studies were made in their work, however.

Our data indicate that the prothrombin recovery period can be greatly shortened by feeding the fat-soluble extract of alfalfa meal along with bile. The extract used is obviously a mixture of many substances. It contains chlorophyll, carotene, and an undetermined amount of sterols, the latter no doubt activated to some extent by sunlight while the hay was being cured. It seems likely that the extract is a good source of most or all of the known fat-soluble vitamins, including large amounts of vitamin K.

Dam and Schønheyder³ and Almquist and Stokstad¹ report a bleeding tendency in chicks which are maintained on a fat-free diet. The addition to the diet of fat-soluble extracts of alfalfa,¹ hog liver and certain other substances² was found to prevent the appearance of the disease. They believe that a new fat-soluble antihemorrhagic vitamin, vitamin K, is the factor concerned. Dam, Schønheyder and Tage-Hansen⁴ and Quick⁹ have presented data suggesting that a prothrombin deficit is the cause of the bleeding in this disease of chicks. Greaves and Schmidt⁵ have recently found a hypoprothrombinemia in bile fistula rats similar to that reported by Hawkins and Brinkhous in dogs. Feeding of vitamin K cured the disease in their rats.

The evidence available suggests that the bleeding tendency seen in obstructive jaundice and biliary fistula is due at least in large part to a vitamin K deficiency. However, hemorrhagic disease due to a deficiency of this vitamin has not been produced in mammals by simple dietary means. For the present it seems best to accept the prothrombin deficit together with the beneficial effect of feeding bile and alfalfa, and to leave the more complete elucidation of the mechanism to further study.

Conclusions. The bleeding tendency so often seen in patients having obstructive jaundice or biliary fistulae is due to a deficiency in plasma prothrombin. This deficiency is related in part at least to absence of bile in the intestine and is relieved by bile feeding. The beneficial effect of bile feeding is greatly enhanced by supplementing the bile with fat-soluble alfalfa extract, rich in vitamin K.

This work was made possible through the generous coöperation of many members of the Departments of Internal Medicine and Surgery. We are especially indebted to Dr. Frank R. Peterson.

For a preliminary report of this work see *Proc. Soc. Exp. Biol. and Med.*, **37**, 628, 1938.

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COMBINED SYSTEM DISEASE WITHOUT OBVIOUS EVIDENCE OF PERNICIOUS (MACROCYTIC) ANEMIA.

REPORT OF 8 CASES; 1 AUTOPSY.

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SINCE the publication of the article by Russel, Batten and Collier in 1900,¹⁰ it has been known that degenerative changes in the spinal cord (subacute combined degeneration of the spinal cord) may accompany pernicious anemia. The combination is so frequent that for many years the diagnosis of pernicious anemia has been almost immediately presumed in a patient with signs and symptoms referable to the posterior and lateral tracts of the spinal cord. This presumption assumed more weight when it was recognized that such symptoms and signs may develop in patients many years before the appearance of anemia.^{6,9}

In the last decade, however, a considerable number of cases of subacute combined degeneration of the spinal cord have been reported in patients without significant anemia.^{1,8,7,8} When compared with the number of cases with definite evidences of pernicious anemia, such cases are uncommon. Necropsy reports of cases without pernicious anemia are rare and doubts have been cast on the validity of many of the reported cases.¹⁶

The classical triad of pernicious anemia is: a hyperchromic anemia, degenerative changes in the spinal cord and a defective

gastric secretion (achylia gastrica and an absence of the intrinsic factor of Castle). The exact relationship of these three factors^{2,8,13,14} is not known, since the changes in the spinal cord, as stated previously, and the disturbance of the gastric function may precede the blood changes by many years.⁹ It is possible that the degenerative changes in the spinal cord may be related to some as yet unknown factor, independent of the blood changes and the achylia gastrica; as yet the nature of such an unknown factor can be only conjectured. A defect in the absorption of vitamin B is suggested by the fact that most of the reported cases have associated with the conditions which might be accompanied by such a defect.^{11a,b,15} We, therefore, thought it desirable to report this study of 8 cases of subacute combined degeneration of the spinal cord without a macrocytic anemia.

A few words are necessary regarding the methods of diagnosis in these cases reported. Many diseases of the nervous system may produce changes in the posterior and lateral tracts of the spinal cord with a resulting symptomatology closely resembling that of subacute combined degeneration of the cord as seen in pernicious anemia. Only a few of the more common ones need be mentioned, such as multiple sclerosis, syphilitic meningomyelitis, syringomyelia and spinal cord tumors. To exclude as far as possible the above mentioned diseases as well as pernicious anemia and other conditions, the following tests were made on all of our patients: careful anamnesis, physical and neurologic examination, a thorough study of the blood, gastric analysis after test meals or histamine, lumbar puncture, Roentgen ray of the spine and serologic tests on the blood and cerebrospinal fluid. For convenience of presentation the cases are divided into four groups: 1, cases without evidence of a disturbance of blood formation and with normal gastric acidity; 2, a case without evidence of disturbance of blood formation but with achylia gastrica; 3, cases with hypochromic (secondary) anemia and normal gastric acidity; and, 4, a case with hypochromic (secondary) anemia and achylia gastrica.

Group 1.—Cases Without Evidence of a Disturbance of Blood Formation and With Normal Gastric Acidity:

CASE 1.—Patient M. N. (Hosp. No. 828713), a 47-year-old female, was admitted to the hospital on July 18, 1936, complaining of weakness of legs, staggering gait and numbness of fingers and hands of several months' duration. For 4 months the symptom complex had become progressively worse and she had fallen 3 times. No history of dietary inadequacy could be obtained.

The patient was obese and well developed. The tongue was smooth at the edges. There was marked weakness of the legs and a slight weakness of the arms, particularly the right. The muscles were well developed and there was no evidence of atrophy. There was hypesthesia to touch and pin prick in the right leg and in the right hand. The sense of vibration was lost in the right tibia and diminished in the left. Position sense was impaired in the toes. The deep reflexes in the arms and knees were exaggerated but the ankle jerks were absent. The Romberg test was positive. Stimulation of

the plantar surface of the feet produced a typical Babinski sign on the right and an equivocal response on the left foot. The abdominal reflexes were absent. On two occasions, the hemoglobin content of the blood was 78% (Sahli). The red blood count was 4,230,000 and 4,460,000 per c.mm.; the white blood count was 6100 per c.mm. with a normal differential count. The Hinton test on the serum was negative. Analysis of the gastric juice after a test meal of 50 cc. of 10% alcohol showed 10 degrees of free acidity and 18 of total acidity. The urine was normal. The cerebrospinal fluid was under a pressure of 175 mm. and the response to compression of the jugular veins was normal. The fluid contained 2 white cells per c.mm. The globulin test was negative and the protein content was 44 mg. per 100 cc. The colloidal gold and Wassermann tests on the fluid were negative.

The patient was treated daily with intramuscular injection of 10 cc. liver extract equivalent to 50 gm. of whole liver. After 10 injections, she was able to get out of her bed and walk around the ward. There was a marked increase of the muscular strength of the legs and diminution in the areas of hypesthesia. There was no improvement in the vibration or position senses. The patient was discharged 3 weeks after entry with instructions to return to the outpatient department for further treatment. After 2 injections were given the patient lapsed from treatment until almost a year later when she was readmitted to the hospital for reexamination at our request. In the meantime, she had received no treatment and had carried on her routine household duties as usual. On the second admission on July 17, 1937, the neurologic findings were much the same as they were on discharge 1 year previously. The hemoglobin content of the blood was 80% (Sahli) and the red blood count 4,230,000 per c.mm. The gastric content, removed 20 minutes after the injection of histamine, showed 40 degrees of free acid. A second lumbar puncture gave entirely normal findings.

CASE 2.—Patient C. A. (Hosp. No. S39775), a 63-year-old married woman, was admitted to the hospital on January 20, 1936, complaining of numbness, tingling in the feet, "cramps," numbness of the legs and difficulty in walking, of 3 weeks' duration. She had fallen several times and had been bedridden for a week previous to her hospitalization. For the preceding 6 months, there was urinary urgency, 10 times in the day and 6 to 8 times at night.

Upon examination, it was found that her tongue was smooth and beefy red, that there were numerous discrete, moderately tender enlarged lymph glands of various size in the cervical, axillary and inguinal regions. One of the glands, removed at biopsy, was regarded as showing evidence of Hodgkin's disease. There was a mild degree of arteriosclerosis of the retinal vessels. The muscles of the legs were weak and the heel-shin test was performed with difficulty. The vibration sense was absent below the level of the crest of ilium. Position sense was impaired in the toes and ankles. The deep reflexes were present in the arms but the knee- and ankle jerks were absent. Stimulation of the plantar surface of the feet produced an atypical Babinski response on the right and a normal response on the left. Examination of the blood on 4 occasions showed a hemoglobin content of 80% (Sahli), a red count varying from 4,020,000 to 4,340,000 per c.mm. and a white count from 6400 to 7300 per c.mm. with a normal differential count. The mean corpuscular volume of the red cells was 90.3% and the hematocrit content was 39.2%. The icteric index was 5.0 and the Hinton test on the serum was negative. Analysis of the gastric content showed 20 degrees of free acidity after 100 cc. of 7% alcohol by mouth. The urine contained many white blood cells. Roentgen rays of the spine were normal. The cerebrospinal fluid was under a pressure of 140 mm. and the response to jugular compression was normal. The fluid was clear and colorless and contained no cells. The protein content was 31 mg. per 100 cc. The colloidal gold and Wassermann tests on the fluid were negative. The findings of a

second lumbar puncture were the same as those of the previous puncture excepting the protein content, which was 50 mg. per 100 cc.

For 5 days, the patient was treated daily by intramuscular injection of 10 cc. of liver extract, equivalent to 50 gm. of whole liver and on the 6th day was started on a series of deep Roentgen ray therapy (20 exposures). On her discharge 2 months after admission, patient was greatly improved physically. There was a gradual diminution of the size of the enlarged glands but no change was noted in the reflexes, vibration or position senses.

CASE 3.—Patient M. A. Y. (Hosp. No. 842619), a 65-year-old married woman, was admitted to the neurologic service on December 23, 1936, complaining of chronic constipation and numbness and tingling of fingers and toes of 2 years' duration. She was well developed and well nourished. There was no atrophy of the papillæ of the tongue. The heart was enlarged and there was a moderate degree of sclerosis of the peripheral and retinal vessels. There was a spastic weakness of the muscles of the extremities without any atrophy. The finger-nose and heel-shin tests were poorly performed. Vibration sense was impaired in both legs and absent in the left ankle. The deep reflexes were all greatly exaggerated with bilateral ankle clonus, Hoffmann and Babinski signs. The abdominal reflexes were absent. The results of the examination of the blood on 4 occasions during her stay in the hospital were as follows: the hemoglobin content varied from 80 to 83% (Sahli), the red cell count from 3,890,000 to 4,100,000 per c.mm. with a slight degree of achromia. The mean corpuscular volume was 88%, the hematocrit content 44%, the white blood count 13,000 per c.mm. with a differential count of neutrophils 75%, lymphocytes 19, large mononuclears 4, basophils 1 and eosinophils 1%. Analysis of the gastric contents showed 98 degrees of free hydrochloric acid 30 minutes after 1 mg. of histamine injection. A second gastric analysis showed 17 degrees of free acid in the fasting specimen and 97 degrees in the specimen removed 30 minutes after the injection of histamine. The Hinton test on the serum was negative. Lumbar puncture was performed on 2 occasions. The cerebrospinal fluid was under a normal pressure and the response to jugular compression was normal. The fluids were clear and colorless, contained no cells and had a protein content of 26 and 38 mg. per 100 cc. Colloidal gold and Wassermann tests were negative.

Ten cubic centimeters of liver extract equivalent to 50 gm. of whole liver were given intramuscularly every day for 2 weeks. Under this régime the patient rapidly improved. She was able to get about the ward at the end of the second week, and was discharged 4 weeks after entry very much improved.

Comment. The 3 above cases present the typical neurologic syndrome commonly associated with pernicious anemia. There were paræsthesia in the hands and feet, weakness and ataxia of the extremities and physical signs of involvement of the posterior and lateral tracts of the spinal cord. In none of the 3, however, was there any significant disturbance of the blood formation or achylia gastrica.

In Case 1 there was no associated disease which could explain the symptoms and signs. In the second case, the possibility of any involvement of the spinal cord by the Hodgkin's disease must be considered.^{3,5} No evidence in support of this hypothesis could be obtained. There was no evidence of cord compression on neurologic examination, lumbar puncture or Roentgen ray of the spine.

The age of the third patient (65 years) and the condition of the peripheral and retinal vessels suggest that arteriosclerosis may have played some rôle in the production of the signs and symptoms.

The degree of improvement in Cases 1 and 3 following parenteral treatment with liver extract merits attention.

Group 2. A Case Without Evidence of a Disturbance of Blood Formation but With Achylia Gastrica.

CASE 4.—Patient M. O. N. (Hosp. No. 801517), a married woman, aged 74, was admitted on October 12, 1935, complaining of weakness of legs of 9 months' duration. Her symptom complex became progressively worse, so that in a short time she began to drag her legs and had to keep her eyes on her feet while walking. For 2 weeks before admission she developed spasmodic radiating pains from the thighs downward.

The patient was well developed and moderately obese. The blood pressure was 140/80. Roentgen ray of the spine showed hypertrophic arthritis in the lumbar region. The important positive neurologic findings were: weakness of the legs and toes; absent knee- and ankle jerks; bilateral Babinski signs; hypesthesia below the knees and absence of vibration sense from the clavicles. There was no significant smoothing of the tongue.

The hemoglobin content of the blood was 90% (Sahli), and the red blood count was 4,500,000 per c.mm. The red cells were normal in size and shape. The white blood count was 6550 per c.mm. with a normal differential count. The cell volume was 4.05, hematocrit content 43.74, mean corpuscular volume 96.9 and mean corpuscular hemoglobin content 31.9. The serum Kahn test was repeatedly negative. The urine was normal and the serum non-protein nitrogen was 32 mg. per 100 cc. There was no free acid in the gastric content either before or after the injection of 1 mg. of histamine. The pressure of the cerebrospinal fluid and its response to compression of the jugular veins were normal. The fluid contained 45 mg. of protein per 100 cc. and the colloidal gold and Wassermann tests were negative.

The patient was not treated during her stay in the hospital.

Comment. In this patient, there were outstanding signs of involvement of both posterior and lateral tracts of the spinal cord. There was an achylia gastrica but the blood picture was within the normal limits. The age of the patient (74 years) suggests that arteriosclerosis may have played some rôle in the production of the symptoms and signs.

Group 3. Cases With Hypochromic (Secondary) Anemia and Normal Gastric Acidity.

CASE 5.—Patient H. C. (Hosp. No. 804254), a 67-year-old hotel clerk, entered the hospital on November 7, 1935, with complaints of increasing weakness of legs and difficulty in walking for 9 months' duration. He had some urinary urgency and occasional fecal incontinence for a year or 2 before admission.

Examination showed a rather obese, elderly looking person with marked general weakness, slight sclerosis of the retinal vessels and slightly smoothed papillæ of the tongue. The blood pressure was 140/90. There was ataxia and asynergia of the lower extremities. Vibration and position senses were markedly impaired in the legs. The knee jerks were normally active but the ankle jerks were absent. There was a bilateral Babinski response. The abdominal and cremasteric reflexes were absent. The Romberg test was positive. The blood was examined 9 times during the patient's stay in the hospital. The hemoglobin varied between 76 and 80% (Sahli); the red

count between 3,700,000 and 3,800,000 per c.mm.; the white count between 7550 and 14,000 per c.mm. The differential counts were within normal limits. The hematocrit content was 36.9; the mean corpuscular hemoglobin content 33.8; the mean corpuscular hemoglobin volume 85.6, and the icteric index 3.0. The Hinton test of the serum was negative. Lumbar puncture showed normal findings except for a protein content of 61 mg. per 100 cc. on fluid removed at first puncture and 102 mg. per 100 cc. on that removed 10 days later. The cerebrospinal fluid Wassermann reaction was negative. Gastric analysis before liver treatment showed 12 degrees of free acid and 22 of combined acid in the fasting specimen. Thirty minutes after subcutaneous injection of 1 mg. of histamine there were 96 degrees of free acid and 13 degrees of combined acid. Examinations of the urine were normal. Roentgen ray of the spine showed hypertrophic arthritis in dorsolumbar region.

Fairly intensive treatment by intramuscular injections of liver extract was given to the patient. Two weeks later, he was able to get up and to walk about the ward. At the same time, physiotherapy in form of heat, massage and passive motion was also given to the legs. At the time of discharge on January 16, 1936, patient was greatly improved. Intramuscular injections were continued once a week in the outpatient department and the patient continued to improve slightly until October, 1936, when he was admitted to the hospital on account of symptoms of coronary thrombosis, and died. Unfortunately, the spinal cord was not removed at autopsy.

CASE 6.—Patient B. D. (Hosp. No. 770716), a 46-year-old married negress, was admitted to the hospital on November 10, 1933, complaining of numbness of the hands for 5 years' duration. The symptoms started in the right hand and extended to the left hand after 2 years accompanied by dragging of the left leg. The symptoms became progressively worse so that at the time of her admission, she had great difficulty in executing fine movements of her fingers. One month before her admission, her hands became icy cold. The diet as given by the patient seemed to be well balanced and adequate.

On physical examination there was bilateral interstitial keratitis, slightly saddle-shaped nose, peg-shaped lateral incisors and dystrophic lower teeth. The blood pressure was 135/98. The abnormal findings on neurologic examination were: bilateral deafness of middle ear type; spasticity and weakness of the legs; hyperactive tendon reflexes except for the ankle jerks, which were absent; bilateral Babinski and Hoffmann signs; absent abdominal reflexes; difficulty in recognizing objects with the tips of the fingers; impaired position and vibration sense in the legs. The blood hemoglobin content was 74% (Sahli). The red blood count was 3,550,000 per c.mm. The mean corpuscular hemoglobin content 30.9; mean corpuscular volume 105; icteric index 4.0. The white blood count was 6000 with the differential count as follows: neutrophils 58%; small lymphocytes 17; large lymphocytes 15; large mononuclears 7; eosinophils 1; stippled and undifferentiated forms 2%. Gastric analysis showed 22 degrees of free acid and 33 of combined acid in the fasting specimen. The cerebrospinal fluid was under a pressure of 110 mm. The dynamics were normal. The protein content was 32 mg. per 100 cc. and the colloidal gold reaction was negative. Repeated Wassermann reaction of both blood and cerebrospinal fluid was negative. The urine was normal. Patient left the hospital before treatment could be instituted.

CASE 7.—Patient E. B. K. (Hosp. No. 665464), a married woman aged 37, was admitted to the Neurological Service, Boston City Hospital, on March 11, 1932, because of sudden attacks of crying spells during which time she was confused, irrational, overtalkative, combative, unable to recognize her husband and expressed delusion of persecution. She had 3 similar

attacks in the 2 months before admission. For 3 years before admission, patient had been having melena and losing weight. For 1 year before admission, she suffered from blood in stools and was treated for intestinal worms.

On examination, the patient was greatly emaciated and appeared anemic. The tongue was smooth and red in color. All deep reflexes were greatly exaggerated with bilateral ankle clonus, Babinski and Hoffmann signs. The sensory examination was not entirely satisfactory due to the lack of coöperation. However, the vibration sense seemed to be definitely impaired over the legs and the lower lumbar spine.

The blood hemoglobin content was 48% (Sahli), the red blood count 2,800,000 per c.mm. and the white blood count 13,000 per c.mm. Throughout her 10-month stay in the hospital, the patient's blood was examined at frequent intervals. The blood hemoglobin remained at the level of 40 to 52% (Sahli) with no significant changes in the total red or the differential count. However, there was a considerable variation of the total white blood count ranging from 4100 to 17,750 per c.mm. The red blood cells appeared normal in shape but showed marked achromia and some variation in size. The serum non-protein nitrogen was 46 mg. and the serum sugar content was 100 mg. per 100 cc. The serum Kahn, Hinton and Wassermann reactions were negative. Gastric analysis on admission showed 33 degrees of free acid and 54 of total acid in the fasting specimen. Four days later, there were 55 degrees of free acid and 90 of total acid in the fasting specimen. Throughout her stay in the service, patient ran a septic temperature varying from 96° to 103° F. Repeated blood cultures were negative. Roentgen ray of the chest and the gastro-intestinal tract showed no significant abnormalities. The electrocardiogram was normal. Frequent examination of the urine showed numerous white cells, singly and in clumps. The cerebrospinal fluid was examined on 2 occasions. It was under a normal pressure and the response to compression of the jugular veins was normal. The fluid was clear and colorless and contained no cells. The total protein content was 17 mg. and 23 mg. per 100 cc. and the colloidal gold reactions were 1233211000 and 1111100000. Wassermann reactions were negative. Repeated agglutination tests of the serum with typhoid and paratyphoid organisms were negative.

For the first few days after admission, patient was irrational, over-talkative, emotionally labile, striking at nurses and attendants, spitting on the walls and refusing to take food. She expressed a fear that someone might do harm to her.

The patient remained in the hospital for 10 months and was treated daily for 1 week with intramuscular injections of 10 cc. of liver extract representing 50 gm. of whole liver, together with 4 gm. of vegex 3 times daily and a high caloric, high vitamin diet. There was no change in the general clinical picture, neurologic signs or blood content on this régime nor after transfusion of 500 cc. of citrated blood. A severe degree of cystitis developed which did not respond to forcing fluids, urotropin and bladder irrigation. The patient continued to be noisy and difficult to manage. Frequent elevation of temperature continued and patient died on January 15, 1933, in an extreme degree of emaciation.

Autopsy was performed 4 hours postmortem. The body was that of a very poorly developed and extremely emaciated female adult. The lower lobe of the left lung showed moderate increase of consistence and decrease in crepitation. The loops of ileum were bound together by thin firm fibrous adhesions as the liver and spleen were adherent to the diaphragm. The wall of the sigmoid and rectum was greatly thickened and the muscularis stood out as a translucent milky white. The mucosa was thickened, firm, injected, and furrowed with longitudinal ulcers in a few irregular areas.

Urinary bladder was slightly injected. Kidneys and ureters were negative. There were slight atheromatous changes in the aorta. The spinal cord appeared grossly normal. Sections of the cord stained by the Weigert Pal method showed a moderate degree of degeneration of the myelin in the posterior columns and around the periphery of the cord in the lateral and anterior columns. In the region of the crossed pyramidal tracts, however, there was a marked loss of the myelin.

Comment. Signs and symptoms of involvement of the posterior and lateral tracts of the spinal cord were pronounced in all of these cases. The anemia in Case 5, which was only of a slight degree, was definitely of the hypochromic (secondary) type and the patient responded remarkably well to the liver treatment. In Case 6, there was slight variation in the size and shape of the red blood cells. However, the combination of a normal diet and normal gastric acidity in a negress was considered by medical consultants as making the diagnosis of pernicious anemia extremely unlikely. On the other hand, the saddle nose, the interstitial keratitis and the dystrophic lower teeth, suggested the diagnosis of congenital syphilis. The possibility that the signs and symptoms of spinal cord disease could be explained on this basis was not definitely excluded by the normal spinal fluid and negative blood serology.

In Case 7, there was a marked degree of hypochromic anemia secondary to an ulcerative colitis. The signs and symptoms in the nervous system in this case could readily be attributed to an impairment of the function of the gastro-intestinal tract, with inadequate absorption.

Group 4. *A Case With Hypochromic (Secondary) Anemia and Achylia Gastrica.*

CASE 8.—Patient A. M. B. (Hosp. No. 773232), a married white female aged 45, was admitted on January 14, 1935, complaining of difficulty in walking and a sensation of unsteadiness following a fall in the snow at age of 35. For the past 8 years, she had to walk with the aid of a cane or other support and had gained an unknown amount of weight. The right leg was at the same time growing fatter than the left. During the past 2 years, absence of menstrual flow had alternated with periods of menorrhagia.

On examination, the patient was obese and appeared anemic. The fat was distributed in the form of flabby pads on the trunk and extremities tending to spare the face, hands and feet. The right foreleg was particularly large and was rendered shapeless by the pads of fat which were tender on pressure. The tongue was smooth. The positive neurologic findings were: weakness of the legs, impaired position and vibration sense in the legs, hyperactive tendon reflexes throughout with bilateral Babinski and Hoffmann signs, the finger-to-moving object test was very inaccurately done but the finger-nose test was fairly well performed. Gastric analysis showed no free acidity in the fasting specimen or in the specimen removed after the ingestion of 100 cc. of 10% alcohol by mouth or after the intramuscular injection of 1 mg. of histamine. The combined acidity was 13, 29 and 4 degrees in the 3 specimens respectively. The blood hemoglobin was 56% (Sahli), the red blood count 4,600,000 per c.mm. and the white blood count 4800 per c.mm. The differential count of the blood was within normal limits. The hemotocrit content was 33.1, mean corpuscular hemoglobin

content 26.4, mean corpuscular volume 60.2 and icteric index 2.0. With the institution of liver and iron therapy, the blood hemoglobin rapidly rose to 65% (Sahli) and the red blood count to 5,500,000 per c.mm. The cerebrospinal pressure was normal and the total protein content in the cerebrospinal fluid was 36 mg. per 100 cc. The cerebrospinal fluid Wassermann and the serum Hinton tests were negative. Daily injections of liver extract were given intramuscularly (10 cc. of liver extract representing 50 gm. of whole liver) together with iron administration in the form of Feosol and high vitamin diet, patient was discharged after 5 weeks in the hospital, her neurologic condition apparently not affected by the above treatment.

Comment. In this patient, in addition to a mild degree of hypochromic anemia and achylia gastrica, there were evidences of endocrine dysfunction. The distribution of the fat and its tenderness on pressure were characteristic of the so-called syndrome of *adiposa dolorosa*.

General Comment. In summarizing our cases, it is noteworthy that 7 of the 8 patients were women. The ages varied between 37 and 74 years, divided according to decades as follows: fourth, 1; fifth, 3; seventh, 3; and eighth, 1.

Weakness and ataxia of the legs were the most common symptoms and were present in all of the 8 cases. Paresthesia (numbness and tingling) of the extremities were present in 5 and bladder symptoms in 2.

In the general physical examination, evidence of arteriosclerosis were present in 3 patients, all of whom were in the seventh decade. In the neurologic examination, the ankle jerks were absent in 5 patients, hyperactive in 2 and normal in 1. The knee jerks were absent in 2, hyperactive in 4 and normal in 2 patients. In all of the 8 patients, the plantar responses were of Babinski type and the vibration and position senses were impaired in the lower extremities. A definite loss of cutaneous sensibility was found in only 2 patients.

Roentgen rays of the spine were normal in 6 patients and there was a moderate degree of hypertrophic arthritis in 2. The serologic tests were negative in the blood and cerebrospinal fluid in all 8 patients. The cerebrospinal fluid was under a normal pressure and the response to compression of the jugular veins was normal in all. The only abnormality in the fluid was a slight increase in the protein content in Cases 2 and 5.

Complication factors were present as follows: Arteriosclerosis in Cases 2, 3 and 5; Hodgkin's disease in Case 2; ulcerative colitis and diarrhea in Case 7; glandular dysfunction in Case 8 (? *adiposa dolorosa*).

Liver extract* was given parenterally to 6 of the 8 patients (Cases 1, 2, 3, 5, 7 and 8). Good subjective response as manifested by improvement of strength was obtained in 4 of the 6 patients,

* The extract was prepared in the Thorndike Memorial Laboratories by the method of Strauss, Castle and Taylor.

and in none of the cases treated with liver was there a progression of the neurologic symptoms. These results are in harmony with those obtained by Strauss and his co-workers¹² in patients with combined system disease associated with pernicious anemia.

Discussion. Our cases were analyzed in detail to determine if any factor common to them all could be found. No such factor was found. The most significant facts were that 7 of the 8 patients were women and 4 of the 6 patients who were treated with liver extract were remarkably improved. Hypochromic anemia of a moderate degree was present in 4 patients and achylia gastrica in one of these 4 and in 1 additional patient.

The existence of a common factor in cases with signs and symptoms of subacute combined degeneration of the spinal cord without pernicious anemia can, as said before, only be postulated. Since impaired utilization of vitamin B is the most plausible explanation of the spinal cord symptoms in patients with pernicious anemia and it is probable that the same factor is responsible for the occurrence of such symptoms and signs in patients here reported. The evidence presented here, particularly the response to liver therapy, is suggestive but not sufficient to be conclusive evidence for this hypothesis and it is possible that this type of spinal cord disease is only symptomatic of various disease conditions.

Summary. 1. Eight patients with subacute combined degeneration of the spinal cord are reported. In 4 of them there was no evidence of a disturbance of blood formation and in 4 there was a moderate degree of hypochromic (secondary) anemia. Achylia gastrica was found in 1 of the patients in both of the above groups.

2. Among the complication factors were arteriosclerosis in 3 cases, Hodgkin's disease, ulcerative colitis and glandular dysfunction.

3. A good response to parenteral liver therapy was obtained in 4 of the 6 patients so treated.

4. The etiology of subacute combined degeneration without the so-called "pernicious anemia" is briefly discussed.

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THE SIZE OF THE RED BLOOD CORPUSCLE IN DIABETES MELLITUS.

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IN 1931 Root^{15a} reviewed 48 cases of associated diabetes mellitus and pernicious anemia; again, in 1933, he^{15b} reviewed 31 additional cases. He believes there is an increase in the association of the two diseases and attributes this to the prolongation of life in both diabetes and pernicious anemia as a result of the discovery of insulin and liver therapy. In these reported cases, Root omitted those which failed to fulfill the criteria for a definite diagnosis of pernicious anemia, namely: (1) macrocytic anemia or symptoms of spinal cord degeneration or both; (2) achlorhydria; (3) bilirubinemia; (4) reticulocyte response to adequate doses of liver.

It is a well known fact that diabetes mellitus may cause symptoms quite similar to those found in pernicious anemia. Glossitis and numbness and tingling of the hands and feet are fairly common in diabetes. Achlorhydria was found by Joslin,¹¹ and Bowen and Aaron¹ to be present in 30 to 40% of diabetics and its frequency increased with the age of the patient and the duration of the disease. Anemia, although an uncommon finding in uncomplicated diabetes, may be present and is quite frequent in complicated diabetes.

Root^{15a} states that a large group of borderline cases seen at the Deaconess Hospital were not included in the published cases. In this group of borderline patients, some of the criteria for the diagnosis of pernicious anemia were absent.

Because this type of case was seen rather frequently, and because at times there was some difficulty in diagnosing pernicious anemia in combination with diabetes, it was decided to study the blood of diabetics by means of corpuscular volume. On reviewing the literature, it was found that no such study of the blood had been undertaken in cases of uncomplicated diabetes. Several papers have discussed the changes in the volume of the red blood cell in diabetic coma but most of them are incomplete: in some, no mention is made of the method used to determine the corpuscular volume; and in others the number of cases cited is too small to be of value in drawing conclusions.

It is the opinion of Holler and Kudelka,¹⁰ Foldes,⁴ Detre,² and Hashimoto⁸ that in diabetic coma the mean volume of the red blood cell is increased and the diameter of the cell is decreased. Detre states that the volume of the red blood cell is increased in proportion to the degree of acidosis, the maximum volume being reached in coma. Holler and Kudelka, likewise, think that the degree of acido-

sis determines the volume of the erythrocyte. They also believe that if carbon dioxide is passed through a sample of the blood, the diameter of the red blood cells becomes smaller and the cell becomes more spherical in shape.

None of the above mentioned authors states what specific substance in the blood stream during acidosis causes this change. One is led to believe from their discussions that an increase in acidity of the blood causes the changes in the erythrocytes.

Method. All diabetic patients admitted between March 10, 1935, and April 10, 1935, to the New England Deaconess Hospital and George F. Baker Clinic, who were on the service of Dr. Joslin, were considered for this study. The blood determinations which will be described later were made solely on patients who were found, on routine history, physical examination and laboratory work, to be free of any associated disease or any complication of diabetes other than diabetic acidosis or diabetic dwarfism. The 49 selected patients are grouped in Tables 1, 2 and 3; 15 additional cases of diabetic acidosis are grouped in Table 2A. These cases were admitted to the Metabolic Ward of Johns Hopkins Hospital.*

The routine followed in the study of the blood in all of these cases at the Deaconess Hospital is as follows: red blood cell counts, hemoglobin and hematocrit determinations. Urine which was voided not more than 2 hours before or after the blood specimen was taken, was tested for diacetic acid and acetone. The carbon dioxide combining power was determined in any case suspected of having acidosis. Blood-sugar values were determined in 30 uncomplicated diabetics, and all cases of diabetic acidosis and diabetic dwarfism. Venous blood was used for blood studies, 5 cc. being collected in an absolutely dry syringe and put into a small bottle which contained 6 mg. of ammonium oxalate and 4 mg. of potassium oxalate.⁹ Two or more red blood-cell counts were made on each specimen of blood. No figures were used for red cell counts unless they checked within 100,000, in consecutive counts. The average of the counts which checked is the figure used to represent the red blood cell count of that specimen. The hematocrit determinations were made with the Wintrobe^{10a,b} hematocrit, according to his specifications. The centrifuge used was a large electric type which would spin at about 4500 revolutions per minute. The centrifuge was run at its full speed, and checked several times during the study to be sure that packing of the red blood cells was complete. Hemoglobin determinations were made on a Dubosq colorimeter, a Newcomer disk being used for the standard.

There are sixty-four cases in this study and they are presented in three groups: Table 1—uncomplicated diabetes; Tables 2 and 2A—diabetic acidosis; and Table 3—diabetic dwarfs. In each table the cases are arranged in the order of decreasing corpuscular volumes.

Results. 1. Of 42 cases of uncomplicated diabetes mellitus (Table 1) 6 (14.3%) have a corpuscular volume of 95 cu. μ , or over; 11 (26.1%) have a corpuscular volume of 93 cu. μ , or over.

2. Tables 2 and 2A are composed of 18 cases of diabetic acidosis. The 3 cases in Table 2 are children; the 15 in Table 2A are adolescents and adults. Two of the children were found to have corpus-

* I am greatly indebted to Dr. J. E. Howard, who gave me the data on some of these patients.

cular volumes of 84 cu. μ and 85 cu. μ , respectively; 1 was found to have a corpuscular volume of 75 cu. μ . Each of these children had marked diabetic acidosis.

TABLE 1.—UNCOMPLICATED DIABETICS.

Case No.	R.B.C., millions/ c.mm.	Hbg., gm./1000 cc.	Volume packed R.B.C., cc./100 cc.	Corpuscular volume, cubic microns.	Corpuscular hbg., micro micrograms.	Mean corpuscular hbg., conc., %.	Mean cell diameter, microns.	Mean cell thickness, microns.	Blood sugar, mg. %.	Diabetic acid and acetone urine.	Age.	Sex.
1	1.45	15.3	42.0	96	35	36	290	0	25	F
3 D	1.43	15.3	42.0	95	35	36	0	0		
4 W	3.81	..	39.0	102	7.12	2.56	..	0		
5 W	1.59	..	39.0	85	0		
2	4.58	14.8	45.1	99	32	33	220	0	73	M
21 H	4.43	14.2	41.3	93	32	35	0		
3	5.67	19.5	55.8	98	34	35	0	57	M
3 W	5.20	14.2	49.2	95	27	29	0		
3 W, 1 D	5.20	..	49.0	94	7.61	2.08	..	0		
4	1.32	12.5	41.5	96	29	30	80	0	36	F
5	1.93	15.8	46.5	94	32	34	90	0	58	M
24 H	1.95	15.3	47.0	95	31	33	0		
6	5.27	15.8	50.1	95	30	32	160	0	49	M
24 H	5.42	16.2	48.5	90	30	32	150	0		
7	1.03	11.0	38.0	94	29	29	120	0	71	M
8	4.91	15.8	46.0	91	32	31	90	0	53	M
9	4.43	14.2	41.0	93	32	35	120	0	39	F
10	4.49	14.5	41.7	93	32	35	110	0	28	M
11	4.82	15.6	45.0	93	32	35	0		
12	4.99	14.2	45.7	92	29	31	0	48	F
13	5.02	15.3	45.9	92	31	33	110	0	55	F
14	4.73	15.8	43.4	92	33	36	240	0	56	M
15	5.22	14.9	47.6	91	29	31	180	0	41	F
16	4.73	15.3	43.2	91	32	35	170	0	52	M
17	4.76	15.9	43.5	91	33	37	160	0	80	M
18	4.96	14.2	44.6	90	29	32	260	0	20	F
19	5.34	16.1	48.0	90	30	31	0	48	F
21 H	5.36	16.2	48.5	90	30	33	0		
20	3.99	12.2	36.0	90	31	34	200	0	56	F
21	4.27	11.9	38.1	89	28	31	0		
22	4.77	13.0	42.0	88	29	32	180	0	41	M
23	4.46	11.3	39.0	88	25	29	270	0	24	F
24	4.96	14.0	43.4	88	29	33	0		
25	5.54	15.3	48.3	87	28	32	240	0	38	M
26	5.41	15.6	46.4	86	29	34	230	0	55	F
24 H	5.55	16.0	46.8	84	29	34	0		
27	5.01	14.4	43.1	86	29	33	220	0	57	F
28	5.08	15.6	43.5	86	31	36	170	0	27	M
29	4.61	13.8	39.2	86	30	35	222	+	34	F
30	4.72	13.0	40.0	85	28	33	0		
31	4.80	14.8	40.6	85	31	36	150	0	60	M
32	5.63	15.8	47.0	84	28	34	80	0	19	M
33	4.74	15.3	39.8	84	32	38	270	0	75	F
34	4.92	14.9	41.5	84	30	36	0	42	M
35	4.95	13.8	41.2	83	28	34	0	43	M
36	5.29	15.0	44.0	83	25	34	0	30	M
37	5.43	15.2	45.0	83	28	34	0	29	M
38	5.77	17.4	48.0	83	30	36	140	0	18	M
39	5.46	15.6	44.5	82	29	35	290	0	23	F
40	5.27	14.7	43.2	82	28	34	0	39	F
41	6.17	18.0	50.0	81	29	35	110	0	26	M
42	5.49	15.4	43.5	79	28	35	220	0	19	M

H = Hours; D = Days; W = Weeks; M = Months.

Of the 15 cases in Table 2A, 7 (46.6%) were found to have a corpuscular volume of 95 cu. μ , or over, and 11 (73.3%) were found to have a corpuscular volume of 93 cu. μ , or over, at the time of acidosis. If, however, we consider each readmission of Cases 55 and

TABLE 2.—DIABETIC ACIDOSIS (CHILDREN).

Case No.	R.B.C., millions/ c.mm.	Hbg., gm./1000 cc.	Volume packed R.B.C., cc./100 cc.	Corpuscular volume, cubic microns.	Corpuscular hbg., micro micrograms.	Mean corpuscular hbg., conc., %.	Carbon dioxide combining power.	Diabetic acid and acetone urine.	Blood sugar mg. %.	Years of diabetes.	Age.	Sex.
43	4.49	13.3	38.3	85	30	35	9	+++	340	-1 mo.	6	F
24 H.	4.50	13.2	40.0	89	29	33	..	+				
96 H.	4.45	12.6	39.0	88	28	32	Normal	+				
44	5.01	14.2	42.0	84	28	34	22	+	316	2 yrs.	11	F
48 H.	5.37	15.3	45.0	84	28	34	..	0	110			
96 H.	5.09	13.9	45.1	89	27	31	..	0				
6 D.	5.23	13.9	46.3	89	27	30	Normal	0				
45	6.03	14.5	45.0	75	24	32	14	+	230	-1 yr.	13	F
48 H.	5.23	13.9	38.0	73	27	37	..	+				
5 D.	4.80	11.9	42.0	88	25	28	..	0				
7 D.	5.04	12.8	41.5	83	25	31	40	0				

TABLE 2A.—DIABETIC ACIDOSIS (ADULTS).

Case No.	R.B.C., millions/ c.mm.	Hbg., gm./1000 cc.	Volume packed R.B.C., cc./100 cc.	Corpuscular volume, cubic microns.	Corpuscular hbg., micro micrograms.	Mean corpuscular hbg., conc., %.	Carbon dioxide combining power.	Diabetic acid and acetone urine.	Years of diabetes.	Age.	Sex.
46	4.83	..	53.4	111	11.7	++++	..	32	M
6 H.	4.72	..	43.7	93	13.5	++++			
12 H.	4.72	..	41.2	88	57.9	0			
24 H.	3.06	..	29.0	93	65.5	0			
47	5.02	..	55.0	109	7.1	++++	4+	47	F
19 D.	3.00	..	34.5	115	?	0			
48	4.38	11.0	48.1	110	26	23	13.0	++++	2	21	F
49	4.30	12.1	48.0	98	25	25	25.8	++++	2½	17	F
50	4.80	..	46.9	98	29.6	+	M
5 H.	4.65	..	42.6	92	?	0			
16 H.	4.57	..	37.6	82	57.9	0			
4 D.	4.67	12.4	37.1	80	..	33	Normal	0			
51	5.74	..	55.4	97	12.6	++++	-1	17	F
24 H.	4.75	..	45.0	95	39.0	0			
52	5.00	..	48.0	96	27.7	+++	..	26	M
53	5.10	15.0	48.0	94	29	31	15.0	++++	1+	36	M
24 H.	4.28	12.1	36.0	84	28	34	41.2	+			
54	5.31	16.0	50.0	94	30	32	28.0	++++	..	46	F
24 H.	4.60	15.6	41.0	89	34	38	42.8	0			
55	4.76	13.8	44.5	94	29	31	39.0	++++	1+	25	M
Readmission											
4 M.	6.30	19.0	54.5	87	30	35	24.5	++++			
56	5.49	..	50.0	91	11.7	++++	..	14	F
12 H.	4.91	..	38.0	77	82.4	0			
Readmission											
1 M.	5.92	..	49.0	83	10.7	++++			
7 H.	4.65	..	37.0	79	31.5	+			
Readmission											
18 M.	5.64	..	52.0	93	14.0	++++	..	16	F
24 H.	4.18	..	39.0	93	43.8	0			
Readmission											
4 M.	3.90	..	35.3	91	43.9	0			
Readmission											
2 M.	5.56	..	45.2	81	24.0	+++			
57	6.50	..	59.1	91	25.8	++++	M
4 H.	5.18	..	42.7	83	46.6	+			
58	5.50	14.9	48.0	87	27	31	13.5	++++	6	24	F
3 D.	4.52	14.2	41.7	92	31	34	51.4	++			
59	7.10	19.0	56.0	79	28	35	14.6	++++	5	21	F
36 H.	4.19	13.5	37.0	88	32	36	35.3	++++			
60	5.30	..	46.0	87	24.0	++++	-1	24	M

56 as a single case, then there would be a total of 20 cases, 35% of these having a corpuscular volume of 95 cu. μ , or over, and 55% a corpuscular volume of 93 cu. μ , or over.

TABLE 3.—DIABETIC DWARFS.

Case No.	R.B.C., millions/ c.mm.	Hbg., gm./1000 cc.	Volume packed R.B.C., cc./100 cc.	Corpuscular volume, cubic microns.	Corpuscular hbg., micro micrograms.	Mean corpuscular hbg., conc., %.	Blood sugar, mg. %.	Diabetic acid and acetone urine.	Years of diabetes.	Age.	Sex.
61	3.96	13.3	37.8	96	34	35	180	0	7	19	F
7 D	4.34	14.2	39.9	92	33	36					
62	3.94	12.6	36.0	92	32	35	200	0	11	14	M
63	5.52	15.1	49.7	90	27	30	190	0	15	21	F
64	4.66	12.4	39.5	85	27	31	..	0	7	13	M

3. Blood studies on 4 diabetic dwarfs are recorded in Table 3. Each of these patients had very large livers; in 3 instances the liver reached the umbilicus, and, in 1, it was about 1 inch above the umbilicus. In only 1 of these 4 patients was the corpuscular volume found to be above 95 cu. μ . The highest value found in any of the other 3 was 92 cu. μ .

Discussion. The volume of the red blood cell was found to be 95 cu. μ , or above, in 14.3% of 42 uncomplicated diabetics. If, as Wintrobe^{10c} found, the mean corpuscular volume in the normal person is only 95 cu. μ , or above, once in 49 instances, then the mean corpuscular volume in uncomplicated diabetes was 95 cu. μ , or above, 7 times more often than in the normal person.

The diameter of the red blood cells was measured, and, from these measurements, the thickness of the cells was computed in 2 instances (Cases 1 and 3, Table 1). The diameter of the red cells was found to be within normal limits in both cases, 7.12 μ and 7.64 μ , respectively. The cell thickness was slightly increased in both instances, 2.56 μ and 2.08 μ , respectively. Although there are only 2 cases, far too few to draw conclusions, the results support the work of Holler and Kudelka¹⁰ and Hamburger.⁷ Paxton,¹⁴ however, measured the cell diameter in 2 cases of diabetic acidosis and found the diameter to be slightly increased. It is his opinion that the shape of the cell is not changed in diabetic acidosis.

Presumably, there is some substance present, or some change in the already existing substances in the blood of diabetics, which occasionally influences the shape and corpuscular volume of the red blood cells.

In only 1 instance (Case 29) was diacetic acid or acetone found in the urine of an uncomplicated diabetic at the time the blood study was made. In this instance the corpuscular volume was well

within normal limits. It is, therefore, unreasonable to attribute the changes in the red blood cells of uncomplicated diabetics to acidosis. The blood sugar appeared to have no relation to the corpuscular volume. Blood sugars were done on 30 of the 42 uncomplicated diabetics and were found to be low as well as high when the corpuscular volume of the red cell was either below 85 cu. μ , or above 95 cu. μ (Fig. 1).

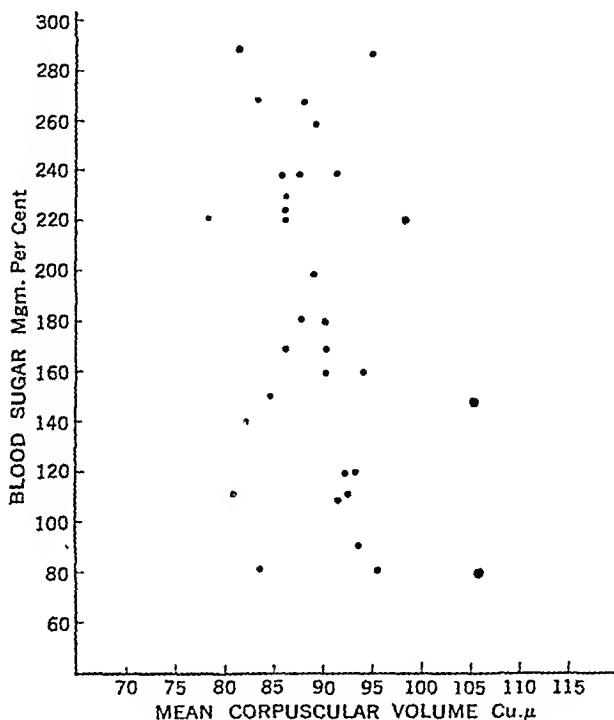


FIG. 1.

Normal values for mean corpuscular volumes in children between the ages of 3 and 13 years, are given by Osgood^{12,13} as averaging 73 cu. μ \pm 3. Guest^{5,6} gives a slightly higher figure, 78 cu. μ to 80 cu. μ . The normal value given by both Guest and Osgood is somewhat lower than Wintrobe's^{16a} average normal value for the adult, 82 cu. μ to 92 cu. μ .

Accepting these values for children as normal, then 2 of the children (Cases 43 and 44, Table 2) were found to have corpuscular volumes slightly above normal. The mean corpuscular volume of 1 child (Case 45) was about normal. There was diacetic acid and acetone present in the urine in all 3 cases and the carbon dioxide combining power was quite low. In each, as the acidosis became less, the corpuscular volume actually increased.

Considering the cases readmitted (Cases 55 and 56, Table 2A) as individual cases, 35% of 20 adults with diabetic acidosis were found to have the corpuscular volume above 95 cu. μ .

In this group of adults with diabetic acidosis, there is no relation between the mean corpuscular volume and the degree of acidosis, as evidenced by the carbon dioxide combining power and the

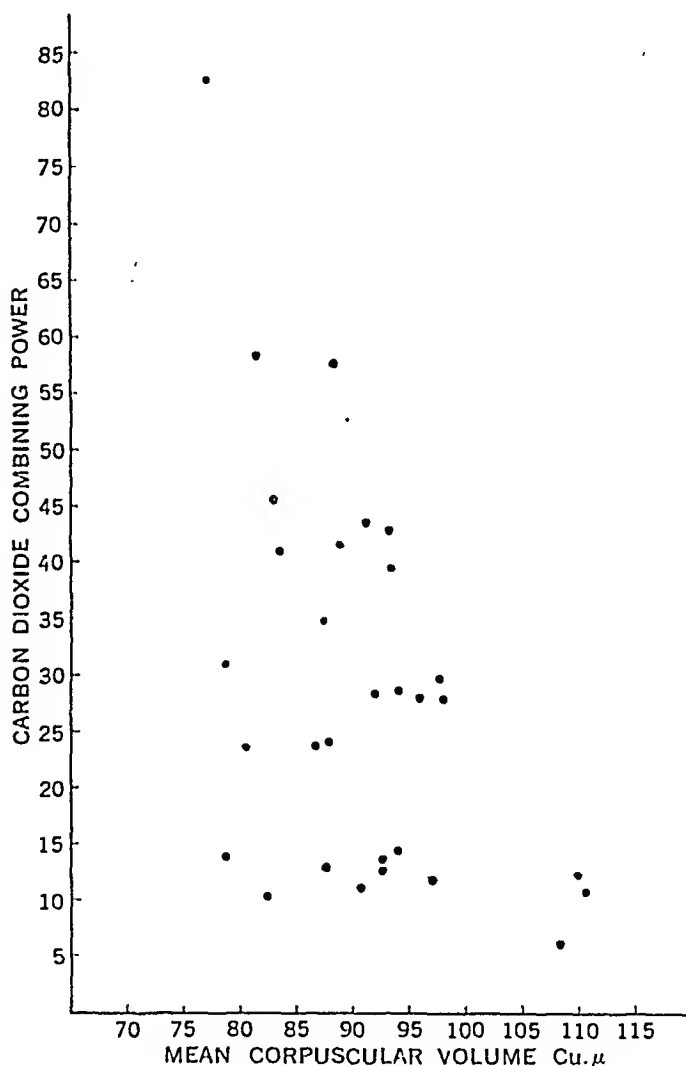


FIG. 2.

presence of diaetic acid and acetone in the urine. Case 55 was admitted to the hospital on 2 occasions. At the time of the first admission, the carbon dioxide combining power was 39 and there was considerable diaetic acid and acetone in the urine. At this time, the mean corpuscular volume was found to be 94 cu. μ . Four months later, the patient was readmitted and, at this time, the carbon dioxide combining power was lower: 24.5. Again there was con-

siderable diacetic acid and acetone in the urine. The corpuscular volume of the red cells at this time was also lower: 87 cu. μ . Because of the patient's lack of coöperation in her own treatment, Case 56 has been readmitted many times. In this case, also, there is no relation between the degree of acidosis and the mean corpuscular volume (Fig. 2).

If, then, the actual degree of acidosis does not affect the volume of the red blood cells in diabetes, what other factor does affect the corpuscular volume? Why should the same individual in acidosis at one time have a slightly elevated corpuscular volume, and, at other times, also in acidosis, have a normal corpuscular volume? It is interesting to note that Elias and Kaunitz³ demonstrated a change in the average volume of the red blood cells in rabbits which were subjected to a lack of oxygen. They did this by keeping the rabbits in an air pressure which corresponded to an altitude of 5000 to 6000 meters. They found the corpuscular volume to increase from the average normal of 65 cu. μ to 87 cu. μ when the rabbits were subjected to the low oxygen tension. These rabbits, on another occasion, were again subjected to a low oxygen tension, but this time were fed carbohydrates during their exposure to the low tension. The corpuscular volume, when carbohydrates were given, remained normal.

Could it be possible that this is the factor which is of importance in diabetics? Children frequently go into coma suddenly, having probably been on a normal diet up to that time. The adults who are found to have a normal corpuscular volume may have been on moderately high carbohydrate diets and adhered to their diet. Those who are found to have a higher corpuscular volume may have been on high-fat diet or may have decreased their carbohydrates and added more fat to their diet.

In view of the fact that the intake of carbohydrate has considerable effect on the water balance and protein metabolism, is it possible that a combination of these factors, rather than acidosis *per se*, influences the mean volume of the red blood cells?

The 4 cases in Table 3, the diabetic dwarfs, were included in this paper only because these cases had enlarged livers. In only 1 instance was the corpuscular volume found to be above the normal value.

Summary. Studies of the red blood cell counts, hemoglobin and hematocrit determinations have been made in 42 cases of uncomplicated diabetes mellitus, 18 cases of diabetic acidosis, and 4 cases of diabetic dwarfism.

The mean corpuscular volume was found to be 95 cu. μ , or above, in 14.3% of the uncomplicated diabetic and in 35% of the cases of diabetic acidosis. This increase in corpuscular volume of the red blood cells could not be attributed to the acidosis *per se*.

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DIFFERENTIAL DIAGNOSIS OF TRAUMATIC ANEURYSM AND ARTERIOVENOUS FISTULA.

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THE physical phenomena associated with arteriovenous fistula are almost pathognomonic for the lesion, yet, "traumatic aneurysms" involving medium sized arterics introduce real problems in differential diagnosis. A history of trauma and a local thrill and bruit are similar and common to both conditions. Significant cardiac enlargement, wide arterial pulse pressure and Branham's¹ phenomenon are cardinal signs observed in an arteriovenous communication; however, at times, because of the small size of the involved vessels or the fistulous opening, these associated alterations in the cardiovascular apparatus are not sufficiently evident to be of diagnostic significance. In a recent study⁴ it was shown that there is a definite elevation of venous pressure and a marked increase in the velocity of blood flow in the veins leading from the fistulous connection to the heart. During the progress of this study there were observed patients who had pulsating masses accompanied by continuous bruits and thrills and histories of regional injury similar in nature to the usual accidents leading to arteriovenous fistula, and in whom the differentiation from traumatic aneurysm was seemingly impossible with the use of the established physical phenomena. It became apparent that the use of venous pressure estimations and velocity of blood flow in the vein proximal to the fistulous connection offered a simple, yet definite, method of differentiating traumatic arteriovenous fistula from aneurysm.

Methods. The venous pressure determinations were made by the technique and with the apparatus of Moritz and vonTabora.³

The velocity of blood flow was measured with the use of the sodium cyanide method of Robb and Weiss.⁵

The following cases have been selected to illustrate the application and significance of this method of differential diagnosis in traumatic arterial lesions.

CASE 1.—A white male, aged 31, who 6 weeks previously was in an automobile accident, sustained from a piece of windshield glass a stab wound at the cubital fossa of the left arm. Soon thereafter he noticed a pulsating mass in the area over which he felt a "peculiar sensation." He was referred for treatment with the diagnosis of a traumatic arteriovenous fistula.

Physical Examination. In the left cubital fossa there was a pulsating mass, approximately 3 by 2 cm. in size, over which a continuous thrill was noted by palpation and a continuous bruit with a definite systolic accentuation by auscultation. The neighboring veins were moderately dilated. The blood pressure was systolic 130 mm. Hg. and diastolic 75 mm. Hg. When the pulsation and thrill were abolished by pressure, the pulse did not slow, which was a negative Branham's phenomenon, nor was there a significant change in the arterial blood pressure. The teleroentgenogram showed the heart to be 13.4 cm. in transverse diameter with a cardiothoracic ratio of 51%. The venous pressure estimation and velocity of blood flow, using the median basilic vein both on the right and left (involved side), are shown in Fig. 1.

Operation demonstrated a traumatic aneurysm of the brachial artery 1 cm. above its division. There was no arteriovenous communication.



CASE 1	ANEURYSM-TRAUMATIC LEFT BRACHIAL ARTERY																							
VENOUS PRESSURE	CIRCULATION TIME IN SECONDS (SODIUM CYANIDE)																							
60 mm. H ₂ O	RIGHT BASILIC																							
																								
55 mm. H ₂ O	LEFT BASILIC																							
																								

FIG. 1.—Circulation time in seconds and venous pressure in millimeters of H₂O.

CASE 2.—A negro male, aged 28, was referred with a provisional diagnosis of syphilitic aortitis with aortic regurgitation and a pulsating mass in the right popliteal fossa. The patient stated that he had been having cramps in the leg precipitated by effort for a period of about 6 weeks. He had noticed a swelling in the popliteal area for about 4 weeks, and for 2 weeks the knee had been stiff and painful. The right ankle had been slightly swollen since the development of dysfunction in the right knee. The past history was not significant with the exception of an ice-pick stab wound located in the inner aspect of the right knee, which he stated had penetrated very deeply into the knee.

Physical Examination. Located in the right popliteal fossa there was a pulsating non-tender tumor over which there were a distinct systolic thrill and bruit, but there was a difference of opinion as to whether the bruit was continuous in type with a systolic accentuation. The veins below and around the right knee were moderately dilated. The heart was definitely enlarged to physical examination, and the teleroentgenogram showed the

cardiac shadow to be 15.6 cm. in transverse diameter with a cardiothoracic ratio of 54%. A systolic murmur was heard over the aortic area and a characteristic diastolic murmur of aortic regurgitation in the same area and down the left sternal border. The arterial blood pressure was systolic 140 mm. Hg and diastolic 60 mm. Hg. Branham's phenomenon was negative; however, the changes in the dynamics of the circulation resulting from the free aortic insufficiency invalidated the significance of the results. The venous pressure estimations and velocity of blood flow in the right and left femoral veins are shown in Fig. 2.

CASE 2	ANEURYSM-RIGHT POPLITEAL ARTERY																						
VENOUS PRESSURE	CIRCULATION TIME IN SECONDS (SODIUM CYANIDE)																						
40 mm. H ₂ O	RIGHT FEMORAL (APEX OF SCARPA'S TRIANGLE)																						
85 mm. H ₂ O	RIGHT BASILIC																						
55 mm. H ₂ O	LEFT FEMORAL (APEX OF SCARPA'S TRIANGLE)																						

FIG. 2.—Circulation time in seconds and venous pressure in millimeters of H₂O.

	CASE 3	ARTERIOVENOUS FISTULA LEFT POPLITEAL ARTERY																					
	VENOUS PRESSURE	CIRCULATION TIME IN SECONDS (SODIUM CYANIDE)																					
FISTULA OPEN	45 mm. H ₂ O	RIGHT BASILIC																					
	80 mm. H ₂ O	RIGHT FEMORAL (APEX OF SCARPA'S TRIANGLE)																					
	245 mm. H ₂ O	LEFT FEMORAL (APEX OF SCARPA'S TRIANGLE)																					
FISTULA CLOSED	125 mm. H ₂ O	LEFT FEMORAL (APEX OF SCARPA'S TRIANGLE)																					

FIG. 3.—Circulation time in seconds and venous pressure in millimeters of H₂O.

Operation demonstrated an aneurysm of the right popliteal artery probably syphilitic in nature.

CASE 3.—A negro male, aged 38, was referred for treatment of an ulcer 3 by 5 cm. located on the lower part of the left leg. The patient stated that 14 years before he was shot in the left popliteal space, the bullet penetrating the thigh. The wound healed promptly. Since then he had worked as a

laborer with no subjective symptoms. The left leg had been moderately swollen for many years, but the ulcer had been present for only 9 weeks.

Physical Examination. There was brawny edema of the lower half of the left leg and a healing ulcer on the inner aspect just above the ankle. The veins below and around the knee were moderately enlarged and distended. In the popliteal space a pulsating, non-tender tumor could be seen and felt. Over the tumor there were a continuous thrill and a continuous bruit, having a systolic accentuation and machine-like quality. When the bruit and thrill were eliminated by pressure, the pulse slowed from 80 to 62 per minute, and the blood pressure increased from systolic 132 mm. Hg and diastolic 70 mm. Hg to systolic 144 mm. Hg and diastolic 82 mm. Hg. The heart was definitely enlarged to percussion and the teleroentgenogram showed the transverse diameter to be 16.2 cm. with a cardiothoracic ratio of 56%. The venous pressure estimations and the velocity of blood flow in the right and left femoral veins with the fistula opened and closed by pressure are shown in Fig. 3.

Operation demonstrated an arteriovenous fistula connecting the left popliteal vein and artery.

Comment. The differential diagnosis in Case 1 was impossible with the use of the usual methods employed in the examination of patients with traumatic aneurysm and arteriovenous fistula. Normal venous pressure and velocity of blood flow in each arm were positive data favoring traumatic aneurysm, the diagnosis confirmed at operation.

Case 2 was most confusing. The history of local trauma, dilated regional veins, and the pulsating tumor in the popliteal space were findings common to both aneurysm and arteriovenous fistula. The aortic lesion resulting in changes in heart size, blood pressure and pulse rate similar to those seen in arteriovenous fistula further confused the differential diagnosis. The venous pressure and velocity of blood flow were slightly lower on the side of the lesion. The difference was not significant, and was accounted for by partial compression of the popliteal vein by the aneurysmal sac.

Case 3 illustrates typically the changes in venous pressure and velocity of blood flow occurring in arteriovenous fistula. The failure of compression to completely restore to normal the venous pressure and rate of blood flow is probably due to the collateral circulation around the fistulous connection. Extensive collateral circulation was demonstrated at the time of the operation, and it is felt that this technique of study may be an index to the degree of collateral blood flow and, therefore, a useful guide to the safety of surgical resection of the connecting artery and vein.

Summary. A technique is described for the positive differential diagnosis of traumatic aneurysm and arteriovenous fistula, and 3 illustrative cases are discussed.

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FALSE-POSITIVE WASSERMANN REACTIONS IN INFECTIOUS MONONUCLEOSIS.

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THERE are several diseases of known etiology, distinct from syphilis, in the course of which serologic tests for syphilis may become temporarily positive. Of this group, the notable members are malaria, yaws, relapsing fever, trypanosomiasis, rat-bite fever, and leprosy. Not infrequently, however, the suspicion of a co-existent latent syphilis is eliminated with difficulty so that the false-positive character of such a Wassermann reaction cannot be indisputably established. Infectious mononucleosis, of unknown causation, typically affects children and young adults in whom the presence of an unrecognized syphilitic infection is reasonably unlikely. It is the purpose of this report to present data concerning 6 cases of infectious mononucleosis in the course of which the complement-fixation, the Eagle flocculation test, or both reactions became temporarily positive. These were discovered among 60 cases of infectious mononucleosis, observed in the past 5 years, in 37 of which one or another of the tests for syphilis was carried out, so that the incidence of transitorily positive serologic reactions was 16%. In all 6 cases to be discussed (Table 1) the diagnosis was established by the clinical course, confirmed by a characteristic blood smear and a positive Paul-Bunnell test.

TABLE 1.—WASSERMANN REACTION AND EAGLE TEST IN 6 CASES OF INFECTIOUS MONONUCLEOSIS.

Case.	Day of disease.	White blood cell count.	Lymphocytes, %.	Sheep-cell antibody titer.*	Complement-fixation test.	Eagle test.
1. I. W.	7	10,000	46	..	44	Negative
	10	1:1024	44	Negative
	16	44444420	Negative
	24	1:256	Negative	Negative
	37	1:64	Negative	Negative
2. W. D.	12	17,200	80	1:2048	44	
	14	15,800	..	1:2048	44	Doubtful
	19	6,200	86	1:512	2244442	Negative
	48	6,800	66	..	Doubtful	Negative
	61	7,080	35	1:64	Negative	Negative
3. R. B.	20	8,750	74	1:2048	Negative	Doubtful
4. M. R.	16	12,250	69	1:1024	024444	Negative
	28	1:2048	Negative	Negative
5. H. B.	10	7,960	75	1:128	44	Positive
	15	11,900	..	1:64	002222	Negative
	17	002222	Negative
	27	7,600	62	1:32	Negative	Negative
6. H. R.	16	16,200	62	..	222000	Positive
	18	11,250	55	1:64	024200	Doubtful
	24	7,040	65	1:32	020000	Negative

* Normal up to 1:16.

Case Reports. CASE 1.—I. W., a white female student, aged 16, whose presenting symptoms were fever and epistaxis, showed on physical examination purpura, a palpable liver and spleen. In view of the platelet count of 72,000 and the positive Paul-Bunnell test, it is assumed that this is one of the rare instances of the thrombocytopenic form of infectious mononucleosis. The Eagle test was negative throughout, while the Wassermann reaction was positive from the 7th to the 16th day of the disease. Within the following 8 days it fell to normal from a high titer of 1 to 150.

CASE 2.—W. D., a white male student, aged 16, whose chief complaints were stiffness of the neck, sore throat and fever, showed on examination follicular tonsillitis, general glandular enlargement and splenomegaly. The Wassermann reaction was positive from the 12th through the 19th day; on the 48th day after the onset of the illness it was doubtful. On one occasion the Eagle test was doubtful; otherwise, it was negative.

CASE 3.—R. B., a white female student nurse, aged 20, who suffered from the anginous variety of the disease, was found to have follicular tonsillitis, general glandular enlargement and an enlarged spleen. A Wassermann test on the 20th day of her illness was negative; the Eagle test was doubtful.

CASE 4.—M. R., a white female student, aged 20, was admitted to the hospital on the 15th day of an illness characterized by fever, headache, vomiting and mild sore throat. Examination showed moderate injection of the pharynx, enlarged cervical, and submental glands and a palpable spleen. On the following day, the Wassermann reaction was strongly positive, the Eagle test negative. At the same time, although the patient had never received typhoid inoculations, there were demonstrated in her blood agglutinins for *B. typhosus* (1:640), *B. paratyphosus A* (1:320) and *B* (1:640). These were present in the same concentration 12 days later, when the Wassermann had become negative coincident with a slight increase in titer of the Paul-Bunnell test.

CASE 5.—H. B., a white male medical student, aged 24, represented one of the more severe cases with intermittent fever to 104° during the first 10 days of the illness. His only symptoms during that period were chills and sweats, followed later by sore throat. Physical findings of note included an injected pharynx, general glandular enlargement and splenomegaly. On the 10th day both Wassermann and Eagle tests were positive. Within 5 days the latter had become negative; the former considerably reduced. In another 12 days the Wassermann, too, was negative.

CASE 6.—H. R., a white male medical student, aged 23, was only mildly ill for 3 weeks with temperature never over 100.4°. The onset was accompanied by pain in the neck, headache and sore throat. Examination on the 16th day showed an injected throat with some exudate, general glandular enlargement and a palpable spleen. Here, again, both Wassermann and Eagle tests were positive over a period of 8 days. It should be noted, moreover, that the Paul-Bunnell test was only moderately positive with a titer of 1:64, in contrast with titers of over 1:1000 in most of the other cases.

Discussion.—In 6 cases of infectious mononucleosis the Wassermann reaction became temporarily positive in 5; the Eagle test positive in 2, doubtful in 2 others. It should be emphasized that the evanescent character of these positive serologic reactions mitigates against the likelihood of recognizing all the instances in which they occur. For example, had Case 5 entered the hospital on the 15th day of the disease rather than on the 10th, a routine Wassermann (not titered) and the Eagle test would have been negative, so that the situation would not have been investigated further. It is

reasonable to assume, therefore, that if these serologic tests were carried out more regularly and persistently, the incidence of positive reactions encountered would be considerably higher than is recorded in the present series. The Paul-Bunnell test may remain positive for 6 months or more. Similarly, the miscellaneous bacterial antibodies that not uncommonly appear in the blood of patients with infectious mononucleosis (Case 4) typically persist for many months while the longest duration of a positive Wassermann was 9 days (Case 1); of the Eagle test even a briefer period.

Scattered references to the occurrence of false-positive Wassermann or allied tests in infectious mononucleosis have appeared. Löhe and Rosenfeld⁶ record the case of a 40-year-old woman who probably suffered from the anginose form accompanied by erythema nodosum. Her Wassermann and Meinicke tests were positive from the 14th to the 74th day of the illness. Radford and Rolleston⁸ report "2 cases of glandular fever simulating typhus" in a mother and daughter both of whom had positive Wassermann's as late as 6 and 8 weeks after the onset of their respective illnesses. That these reactions may have indicated the coëxistence of syphilis is made likely by the failure of the tests to revert to negative within the period of observation, and by the discovery of syphilis in the father. Parkes Weber and Bode⁹ describe 3 cases in whom a temporarily positive Wassermann was observed in all 3, a transitorily positive Meinicke test in 2.

Gooding¹ published an excellent account of an epidemic of infectious mononucleosis which occurred in London in 1930. During the first 3 or 4 weeks of illness, positive or doubtful Wassermann reactions were recorded in 16 of the 27 cases, while a number of these individuals showed positive Kahn tests as well. Hatz⁵ reported the case of a patient with infectious mononucleosis whose Wassermann reaction was positive on the 10th, 16th and 21st days of the disease and thereafter became negative spontaneously. The Kline test was negative throughout, while the Paul-Bunnell test was positive to a titer of 1:32 during the period when the complement fixation test was positive.

It is plain, then, that in the course of infectious mononucleosis one may encounter serologic reactions indistinguishable from those characteristic of syphilis. In a previous report,² on the basis of our first 2 cases, it was assumed that since the complement-fixation test might become positive, while the flocculation test remained negative, the substance responsible for such a reaction could not be reagin. When later events showed that both tests could be positive, one must conclude that reagin or a closely allied substance, was present in these abnormal sera. That these tests are independent of the presence of the sheep-cell antibodies is evidenced by three facts: first, that partial removal of sheep-cell agglutinins makes the complement-fixation test more positive rather than decreases its strength

(so that any binding effect of these agglutinins upon the sheep red-blood cells to prevent hemolysis is inconsequential);² second, that a positive Wassermann occurred in the presence of low titers of sheep-cell antibodies (Cases 5 and 6) while a negative Wassermann was met with in the individual having the highest titer in our series (1:33,000); third, that sheep-cell antibodies may persist for many months after the Wassermann test has become negative and may even increase in titer coincident with a reversion of the Wassermann to negative (Case 4).

In a previous paper² it was noted that, not infrequently, miscellaneous bacterial agglutinins are encountered in the sera of patients suffering from infectious mononucleosis. More recent cases have confirmed this observation (Case 4). Subsequently Belk¹ described in detail the presence in the blood of a patient with this disease of an isoagglutinin, an autoagglutinin, 4 distinct heteroagglutinins and a rouleau-forming property, thus reemphasizing the versatility of antibody responses in infectious mononucleosis.

It is commonly stated that a false-positive Wassermann reaction may occur in thrombocytopenic purpura, although I can find no specific reference in the literature to such a happening. While the thrombocytopenic variety of infectious mononucleosis is uncommon (1 case in the present series of 60) the possibility suggests itself that these rare instances of purpura with false-positive serologic reactions may rather be examples of infectious mononucleosis with reduced platelets. Case 1 was not recognized as infectious mononucleosis until the positive Paul-Bunnell reaction was reported, so that, had this test not been carried out, the final diagnosis would have been purpura hemorrhagica rather than infectious mononucleosis with thrombocytopenia and a false-positive Wassermann reaction. Whenever, therefore, in the course of any disease a Wassermann, suspected of being falsely positive, is encountered, a Paul-Bunnell test should be performed. Should the latter be positive, this is further confirmation of such a suspicion, but a negative test for sheep-cell agglutinins does not necessarily indicate that the patient suffers from syphilis. In a case of rat-bite fever, recently studied, the Wassermann reaction became temporarily positive without any clinical evidence of syphilis, whereas the Paul-Bunnell test was negative.

The problem of why a person suffering from infectious mononucleosis should occasionally develop a false-positive Wassermann is one of great theoretical interest. But since no certain explanation for the Wassermann reaction in syphilis itself is accepted, one can only suggest by analogy that the causative agent of infectious mononucleosis contains a substance having antigenic properties in common with the *treponema pallida*; or else that this causative agent may liberate from the tissues of the patient a reagin-like material. It is pertinent to recall that among the several organisms that have been suggested as the etiologic factor, at least 3 are protozoal in nature.

Repeated attempts have been made to incriminate Vincent's spirochete, since infectious mononucleosis is so commonly associated with a Vincent's throat infection. Bland³ claims to have produced in rabbits and monkeys, a disease resembling infectious mononucleosis with a protozoön of the genus *Toxoplasma*, isolated from the blood of a human case. Third, Mazet,⁷ in Nice, demonstrated in blood smears from a patient with infectious mononucleosis a pleomorphic organism, sometimes contained within the red cells, which in one of its forms was morphologically identical with the spirochete of syphilis. While the relationship to infectious mononucleosis of none of these organisms has been proved, the fact that the majority of diseases which may be associated with a false-positive Wassermann are caused by protozoa, would suggest that the causative agent of infectious mononucleosis may likewise be a protozoön.

Summary.—Transitorily positive serologic tests for syphilis were encountered in 6 out of 37 cases of infectious mononucleosis. During the acute stage of the disease the Wassermann test, the Eagle test, or both reactions became positive to high titers but spontaneously reverted rapidly to negative. These positive tests are independent of the presence of sheep-cell antibodies in the patient's serum and indicate, as does the occasional occurrence of miscellaneous bacterial antibodies, the versatility of antibody responses in infectious mononucleosis. In any instance of apparent purpura hemorrhagica with a false-positive Wassermann reaction a Paul-Bunnell test should be performed in order to establish the possible diagnosis of the thrombocytopenic variety of infectious mononucleosis. Reasons are stated for suspecting that the causative agent of infectious mononucleosis may be a protozoön.

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TUBERCULOSIS OF INTESTINES IN TUBERCULOUS ANTHRACOSILICOSIS.

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ANTHRACOSILICOSIS is frequently complicated by pulmonary tuberculosis. In his study of 418 anthracite coal miners treated at this Sanatorium, Sokoloff¹⁰ states that 237 (56.7%) had pulmonary

tuberculosis. Among 100 cases of anthracosilicosis which came to necropsy at the Sanatorium, Dr. Walsh¹² found evidence of pulmonary tuberculosis in 86. In view of the high prevalence of pulmonary tuberculosis in anthracosilicosis, a study of the frequency with which intestinal tuberculosis may occur in patients with the combined diseases should be of value.

The present communication reports the incidence of intestinal tuberculosis in tuberculous anthracosilicosis and all statements in regard to anthracosilicosis presuppose the presence of tuberculosis. The incidence and extent of the intestinal involvement and their relationship to the degree of anthracosilicosis, type of pulmonary tuberculosis, and the age of the cases are described. The above findings are compared with those in pulmonary tuberculosis uncomplicated by anthracosilicosis.

Material Studied and Findings. Between May, 1934, and December, 1937, a complete postmortem examination was made on 42 cases of anthracosilicosis associated with pulmonary tuberculosis and on 75 cases of non-anthracosilicotic pulmonary tuberculosis.

Among the 42 cases of anthracosilicosis, 8 (19%) had intestinal tuberculosis. Of the 75 cases of non-anthracosilicotic pulmonary tuberculosis, 38 (51%) had intestinal tuberculosis.

Arranged in two main age groups, 6 cases of anthracosilicosis were below 30 years; the rest were between 30 and 65. Of the 6 cases below 30, 4 (67%) had intestinal tuberculosis; of the 36 above 30, 4 (11%) had intestinal tuberculosis. Among the 75 cases of non-anthracosilicotic pulmonary tuberculosis, 45 were below the age of 30, whereas 30 were between 30 and 70. Of the younger group, 24 (53%) had intestinal tuberculosis, while among the older group 14 (47%) had intestinal tuberculosis.

Arranged according to the extent of anthracosilicosis, 14 cases had early or moderately advanced and 28 cases had far advanced anthracosilicosis. Of the early or moderately advanced group, 6 cases (43%) had intestinal tuberculosis, whereas in the far advanced group only 2 (7%) had involvement of the intestines.

Grouped according to the type of pulmonary tuberculosis complicating anthracosilicosis, 9 cases (64%) of the 14 early or moderately advanced group had acute caseous lesions, whereas 5 (36%) had fibrotic lesions. Of those having caseous pulmonary lesions, 4 (44%) showed intestinal tuberculosis, while of those having fibrotic lesions 2 (40%) had intestinal involvement.

Among 28 cases of far advanced anthracosilicosis 3 (11%) had acute caseous pulmonary tuberculosis, while 25 (89%) had fibrotic tuberculosis. One case (33%) of the caseous group and 1 (4%) of the fibrotic group showed intestinal lesions. In only 1 of the above 28 cases was the pulmonary tuberculosis minimal; in the rest it was far advanced with cavitation.

Discussion. The prevalence of intestinal tuberculosis in ordinary pulmonary tuberculosis is a well known fact. McCrae⁷ states that among 1000 Munich autopsies, 566 (56%) showed intestinal tuberculosis. Rubin⁹ found that among his 500 necropsies, 324 (65%) had intestinal tuberculosis. Walsh¹⁰ observed that 76 cases (76%) of his 100 autopsies at the Phipps Institute had involvement of the intestines. Even higher percentages, 80 to 90%, have been reported.³ In the light of the above observations, the relative infrequency of intestinal tuberculosis (19%) in tuberculous anthracosilicosis is striking (Table 1).

TABLE 1.—FREQUENCY OF INTESTINAL TUBERCULOSIS.
Pulmonary Tuberculosis.

	Anthracosilicosis present.		Anthracosilicosis absent.		Combined total.	
	No.	%.	No.	%.	No.	%.
Intestinal tuberculosis present	8	19	38	51	46	39
Intestinal tuberculosis absent	34	81	37	49	71	61
Total	42	100	75	100	117	100

TABLE 2.—FREQUENCY OF INTESTINAL TUBERCULOSIS—ACCORDING TO AGE PERIOD.

	<i>Pulmonary Tuberculosis.</i>											
	Age below 30 years.				Age above 30 years.				Age below 30 years.		Age above 30 years.	
	Anthracosilicosis present.		Anthracosilicosis absent.		Anthracosilicosis present.		Anthracosilicosis absent.		Combined total.		Combined total.	
	No.	%.	No.	%.	No.	%.	No.	%.	No.	%.	No.	%.
Intestinal tuberculosis present	4	67	24	53	4	11	14	47	28	55	18	27
Intestinal tuberculosis absent	2	33	21	47	32	89	16	53	23	45	48	73
Total	6	100	45	100	36	100	30	100	51	100	66	100

It has been recognized that intestinal tuberculosis in pulmonary tuberculosis is more common in the young than in the aged. This is also true in anthracosilicosis associated with pulmonary tuberculosis. Among the miners above the age of 30, only 11% had intestinal tuberculosis, whereas of the younger group 67% showed it (Table 2). The reason appears to be that among the younger miners the degree of anthracosilicosis was less and the pulmonary tuberculosis was more acute. However, age *per se* does not seem to be the determining factor in the incidence of intestinal tuberculosis in the miners.

Table 3 clearly indicates that in early or moderately advanced anthracosilicosis intestinal tuberculosis occurs with practically the same frequency as in non-anthracosilicotic pulmonary tuberculosis. In these cases, pulmonary tuberculosis showed a definite tendency toward rapid spread and destruction. The amount of the intestinal involvement when it occurred was great; often the entire length of the ileum, cecum and other parts of the large bowel were involved. In far advanced anthracosilicosis when intestinal tuberculosis occurred, the lesions, as a rule, were few in number and less extensive.

TABLE 3.—FREQUENCY OF INTESTINAL TUBERCULOSIS ACCORDING TO DEGREE OF ANTHRACOSILICOSIS.

Pulmonary Tuberculosis.

Intestinal tuberculosis.	Anthraco-silicosis absent.		Anthracosilicosis present.			
			Early or mod. advanced.		Far advanced.	
	No.	%.	No.	%.	No.	%.
Present	38	51	6	43	2	7
Absent	37	49	8	57	26	93
Total	75	100	14	100	28	100

There is no doubt that intestinal tuberculosis is rare in far advanced anthracosilicosis associated with pulmonary tuberculosis. This, however, does not mean that anthracosilicosis has generally an inhibitory effect upon the development of tuberculosis. On the contrary, Sokoloff¹⁰ found that the incidence of pulmonary tuberculosis increased in direct proportion to the amount of anthracosilicosis. He found that in the first stage of anthracosilicosis 5.4%, in the second stage 24%, and in the third stage 70.1% had pulmonary tuberculosis. However, as far as intestinal tuberculosis is concerned, it became rarer as the degree of anthracosilicosis increased.

The rarity of intestinal tuberculosis in the late stage of anthracosilicosis is very probably due to the presence of pulmonary fibrosis and the customary chronicity of the pulmonary tuberculosis in these patients, as observed by Landis.⁵ The cavity when it forms in the center of an anthracosilicotic mass enlarges very slowly. Often such a cavity contains mucoid material having only a few tubercle bacilli or none at all. The cavity wall and the surrounding tissue wall when examined microscopically show very few tubercle bacilli or none at all. Furthermore, the blood-vessels in the anthracosilicotic mass and particularly in the neighborhood of the cavity always undergo extreme sclerosis frequently followed by thrombosis. Blood-vessels completely obliterated by fibrosis are frequently observed.^{2,8} Such vascular changes would tend to prevent the spread of tubercle bacilli.

The pathogenesis of secondary tuberculosis of the intestines in the adult is not clearly understood. It may be due to direct infection

by swallowed sputum which contains tubercle bacilli (Karsner⁴ and MacCallum⁶) or to a spread through the lymphatics (Asehoff¹), or to a hematogenous spread. In our study, all cases of intestinal tuberculosis in either the anthracosilicosis or pulmonary tuberculosis group had repeatedly positive sputum of high Gaffky counts; on the other hand, many cases with such sputum had no intestinal lesions. Three of the 8 cases of anthracosilicosis with intestinal involvement had tubercles in the kidneys as well; in these cases the mode of infection may have been through the circulatory system.

In reference to the symptomatology of intestinal tuberculosis, it was interesting to note that in 5 cases of anthracosilicosis having tuberculosis of the intestines there was no complaint whatever suggesting any intestinal lesion. In 3 cases abdominal pain, tenderness in the right lower quadrant, diarrhea, nausea and vomiting were present singly or together from time to time. Walsh^{11b} has observed that pain, tenderness, diarrhea and abdominal rigidity, which were considered as the classical symptoms of intestinal tuberculosis, possess no definite diagnostic value. His observation held true in the present study.

The common abdominal complaints among the far advanced anthracosilicotic patients with or without pulmonary tuberculosis are anorexia, vague abdominal discomfort, flatulence and diarrhea alternating with constipation. These symptoms may be due to chronic passive congestion of the gastro-intestinal tract secondary to myocardial weakness, which is a common occurrence in anthracosilicosis.

In view of the preponderance of intestinal tuberculosis in early or moderately advanced anthracosilicosis complicated by acute caseous pulmonary tuberculosis, any persistent abdominal complaints together with rapid loss of weight, high and irregular fever may justifiably lead to the suspicion of tuberculous involvement of the intestinal tract.

Summary and Conclusions. 1. Tuberculosis of intestines is infrequent in tuberculous anthracosilicosis.

2. The postmortem examination of 42 cases of tuberculous anthracosilicosis revealed 8 cases (19%) of intestinal tuberculosis. Among 75 cases of non-anthracosilicotic pulmonary tuberculosis, 38 (51%) showed intestinal tuberculosis.

3. Tuberculosis of intestines when it occurs in the presence of anthracosilicosis is most frequently found in early or moderately advanced anthracosilicosis. In this stage the incidence of intestinal involvement is practically the same as in non-anthracosilicotic pulmonary tuberculosis.

4. In the presence of far advanced anthracosilicosis intestinal tuberculosis is uncommon; only 7% of 28 cases showed intestinal tuberculosis. This relative infrequency of intestinal tuberculosis appears to be due to the extensive fibrosis of the lungs, and the

chronicity of the pulmonary tuberculosis usually present in these patients. A combination of these two conditions apparently tends to prevent the spread of tuberculous infection to other parts of the body.

5. The incidence of intestinal tuberculosis was greater among those under the age of 30 in both anthracosilicotic and non-anthracosilicotic groups. But the age *per se* does not appear to be the determining factor; of the anthracosilicotic cases above the age of 30, 11% had intestinal tuberculosis, while of the non-anthracosilicotic group of the same age period 47% showed intestinal lesions.

6. In the majority of cases of intestinal tuberculosis in anthracosilicosis, there were no symptoms referable to the gastro-intestinal tract. Pain, tenderness, and diarrhea which were present in a few cases could not be depended upon for the diagnosis. The vague abdominal discomfort frequently complained of by anthracosilicotic patients may well be due to chronic passive congestion of the gastro-intestinal tract secondary to gradual myocardial failure.

The writers wish to tender their thanks to Dr. Frank A. Craig and Dr. Joseph Walsh for their criticisms and the permission to use the Sanatorium material.

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THE EFFECT OF SODIUM CHLORIDE DEFICIENCY ON GASTRIC ACIDITY.*

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LITTLE is known about the effect of sodium chloride deficiency on gastric secretion. In clinical studies, it has been impossible to select conditions in which the chloride deficiency is uncomplicated. In the

* Supported in part by the Christine Breon Fund for Medical Research.

following study, an endeavor was made to maintain the subjects in as normal a physiologic state as possible except for limited intake and increased output of chlorides.

The earliest work on the effects of salt deficiency on gastric secretion was done by Rosemann^{7a} in 1911. He placed one dog on a salt-free diet, and found that the free hydrochloric acid in the gastric juice diminished gradually to zero. It is questionable whether his data justify his conclusions. Takata⁸ (quoted by Rosemann) could not confirm these results experimentally. Rosemann^{7b} in a later paper attempted unsuccessfully, it appears to the writer, to reconcile his conclusions with those of Takata. Pruin,⁴ using dogs with a Pavlov pouch, found that a low salt diet caused diminution of gastric juice and a decrease in hydrochloric acid, although the total chlorides remained the same. In later experiments, Dragstedt and Ellis² showed that in dogs rendered hypochloremic the amount of free and total hydrochloric acid as well as the total chlorides in the gastric secretions remained normal almost to the point of death of the animals.

Eimer³ found that when normal people were placed on a low salt diet, the gastric hydrochloric acid remained normal or increased. A tendency to a rise in free and total hydrochloric acid was noted by Unverricht¹¹ in similar experiments. None of the workers who have studied heat-cramps has reported on the hydrochloric acid secretion of the stomach in this condition. Talbott⁹ examined the vomitus of 1 patient and found a chloride concentration of 135 mg. per 100 cc. Blood taken shortly before the patient vomited had a serum chloride concentration of 339 mg. per 100 cc. McCance⁶ has recently reported the effect of uncomplicated sodium chloride deficiency in man but he did not examine the gastric secretion of his subjects.

Method. The method used in our experiments to produce sodium chloride deficiency followed closely that which was introduced by McCance.⁶ Three normal, healthy, adult male volunteers were the experimental subjects: M. H. S., age 29; J. B. L., age 30; and J. C. L., age 27. All 3 continued to perform their usual duties throughout the experiment. Gastric analyses were made each morning at 8 o'clock, the subjects having fasted since 9 o'clock the evening before. Smoking was stopped at midnight and was not resumed until after the test each morning. When a stomach-tube had been passed and a fasting sample withdrawn, 50 cc. of a 7% aqueous solution of ethyl alcohol were ingested through the tube. Samples of the gastric contents were taken 20, 40 and 60 minutes after ingestion of the test meal. Following this, 0.1 mg. of histamine hydrochloride per 10 kg. of body weight was injected subcutaneously into the deltoid region and samples of gastric juice were withdrawn 15 and 30 minutes after the injection. The gastric juice was titrated, using Töpfer's reagent and phenolphthalein as indicators.

Specimens of fasting venous blood were taken each morning immediately prior to the gastric analysis. The whole blood chlorides and plasma chlorides were determined by the method of Whitehorn.¹² Determinations of urea nitrogen and non-protein nitrogen of fasting venous blood were made on the last day of the experiment and again several weeks later.

Urine was collected in 24-hour specimens, terminating at 7 o'clock each morning. A few cubic centimeters of chloroform were added as a preservative. The urinary chlorides were determined by the method of Hawk and Bergeim.⁵

A preliminary control period was established in order to determine the results of the laboratory procedures under normal conditions for each individual. Two of the 3 subjects had tests on 3 mornings, and the third on 1 morning. The experimental period began on the day following the control period, lasted 7 days, and had two objectives: 1, to decrease the sodium chloride intake; and 2, to increase the sodium chloride output.

A dietary régime was outlined by a member of the dietetic staff of the hospital. The caloric intake daily was 1800 to 1900 calories, with at least 45 gm. of protein and from 0.7 to 0.9 gm. of sodium chloride. Most of the salt was contained in bread and butter and as these foods were not always eaten, the figures given above represent a maximum intake. Fluids were taken freely, usually in the form of distilled water. A typical diet is shown in Table 1.

TABLE 1.—A TYPICAL DIET USED DURING THE EXPERIMENT.

		Grams.	
Total intake:	0.754	Sodium chloride	
	52	Protein	
	117	Fat	
	243	Carbohydrate	
	2233	Calories	
BREAKFAST:	200	Orange juice	
		One egg	
	60	Salt-free bread	
	15	Salt-free butter	
	15	Jelly	
	30	Pastry cream	
		Coffee	
LUNCHEON	100	Rice or macaroni	
	200	Vegetables from among the following: cabbage, carrots, celery, artichokes, cucumber, string beans, eggplant, squash, tomatoes, corn, peas	
	15	Salt-free mayonnaise	
	30	Pastry cream	
	30	Salt-free bread	
	15	Salt-free butter	
	15	Almonds	
	30	Fresh dates	
	100	Fresh fruit from among the following: apples, apricots, peaches, pears, grapes, figs, strawberries	
		Coffee	
DINNER:	100	Beef, lamb, veal or chicken	
	100	Potato	
	200	Vegetable as at luncheon	
	30	Salt-free bread	
	15	Salt-free butter	
	15	Salt-free mayonnaise	
	30	Pastry cream	
	15	Walnuts	
	30	Raisins	
	100	Fruit as at luncheon	
		Coffee	

During the experiment, several measures were used to increase sweating. The subjects ate, slept and spent as much time as possible in an air-condi-

tioned room, the temperature of which was maintained constantly at 88° F. and the relative humidity at 35%. This atmosphere was not intolerable but resulted in peripheral vascular dilatation. Sweating was moderate and occasionally profuse, especially at night. All 3 subjects spent half an hour during each of the first 4 afternoons of the experimental period in a radiant-heat bath. This apparatus is standard physiotherapy equipment and consists of a metal box open at one end and heated by several rows of 250-watt bulbs. The subject lies on a covered rubber mattress and the open end of the box is then closed with a blanket leaving his head exposed. The temperature inside rises to 120 to 150° F. within a few minutes, profuse sweating results and continues for a varying period of time up to 2 hours in spite of cold needle-showers. There is an average loss of approximately 1½ pounds during this procedure.

TABLE 2.—GASTRIC ANALYSES.

	8/29/36.		8/31/36.		9/1/36.		9/2/36.		9/3/36.		9/4/36.		9/5/36.		9/7/36.	
	Free.	Total.	Free.	Total.	Free.	Total.	Free.	Total.	Free.	Total.	Free.	Total.	Free.	Total.	Free.	Total.
M.H.S.:																
Fasting . .	0	6	10	18	24	38	16	32	12	34	12	34	16	20	24	46
20 min. . .	0	8	26	38	24	34	30	36	24	34	32	38	52	62	44	59
40 min. . .	0	8	44	56	44	56	42	54	40	58	54	64	74	86	56	72
60 min. . .	0	10	0	14	44	60	62	78	60	72	56	68	56	70	30	46
Histamine:																
15 min. . .	0	16	86	98	90	100	78	90	86	94	100	112	96	108	82	96
30 min. . .	0	12	112	124	106	118	102	110	116	126	114	122	50	60	106	116
J.B.L.:																
Fasting . .	0	8	16	28	24	34	14	32	0	22	0	14	0	20	0	10
20 min. . .	48	60	28	38	58	68	32	44	0	14	18	26	34	34	28	38
40 min. . .	32	46	38	44	68	80	32	42	0	12	24	32	42	54	0	16
60 min. . .	34	48	26	38	28	38	20	36	10	32	24	36	34	48	26	38
Histamine:																
15 min. . .	72	84	42	50	82	92	42	52	46	60	46	60	70	82	66	80
30 min. . .	36	50	68	76	80	90	70	92	64	80	86	94	98	104	92	100
J.C.L.:																
Fasting	20	26	0	14	0	14	0	12	0	20	4	12
20 min.	16	62	0	8	8	16	10	20	38	44	18	26
40 min.	24	38	6	16	10	22	8	16	40	50	20	32
60 min.	0	14	0	12	12	28	14	24	14	28	20	34
Histamine:																
15 min.	32	46	14	26	36	48	50	62	44	56	66	80
30 min.	42	58	30	38	90	100	90	100	94	100	94	104

Results. There was no consistent or significant change in the amount of free or total hydrochloric acid secreted by the stomach during the entire experiment (Table 2). Our findings agree with those obtained by Dragstedt and Ellis² in dogs, although the salt deficiency in their animals was more severe. It is difficult to explain the absence of free hydrochloric acid in the subject, M. H. S., on the first day. Gastric analysis 6 years before had been normal. He had a severe histamine reaction but the anaecidity had been noted in the specimens withdrawn before histamine was given.

The gradual decrease of the whole blood chlorides in all 3 subjects is shown in Table 3. While the experimental error of these determinations is 3%, there was found to be a fairly uniform tendency for the whole blood chlorides to decrease on each succeeding day. The daily fluctuations of the plasma chlorides are shown in

Table 4. It is well established that the plasma chlorides are maintained at nearly normal levels until the terminal stages of sodium chloride deficiency are reached. The levels of the urea nitrogen and non-protein nitrogen are given in Table 5.

TABLE 3.—WHOLE BLOOD CHLORIDES.

Date, 1936.	Mg. per 100 cc. as chlorine.			Mg. per 100 cc. as NaCl.		
	M.H.S.	J.B.L.	J.C.L.	M.H.S.	J.B.L.	J.C.L.
8/29 . . .	287	279	...	473	460	
8/31 . . .	295	276	...	486	455	
9/1 . . .	285	276	289	470	455	477
9/2 . . .	283	273	255	467	450	421
9/3 . . .	281	273	261	463	450	431
9/4 . . .	256	270	247	422	447	407
9/5 . . .	251	264	246	414	435	406
9/7 . . .	271	265	252	430.7	437	414

TABLE 4.—PLASMA CHLORIDES.

Date, 1936.	Mg. per 100 cc. as chlorine.			Mg. per 100 cc. as NaCl.		
	M.H.S.	J.B.L.	J.C.L.	M.H.S.	J.B.L.	J.C.L.
8/29 . . .	344	356	...	567	594	
8/31 . . .	361	355	...	595	589	
9/1 . . .	342	344	325	564	570	536
9/2 . . .	328	336	340	541	554	551
9/3 . . .	305	354	345	503	584	569
9/4 . . .	303	341	348	500	562	575
9/5 . . .	326	Broken	339	538	Broken	559
9/7 . . .	341	348	336	562	574	554

TABLE 5.—NON-PROTEIN NITROGEN AND UREA NITROGEN.

Date, 1936.	(In milligrams %.)		
	M.H.S.	J.B.L.	J.C.L.
9/7 Non-protein nitrogen . . .	48.3	36.6	38.7
Urea nitrogen . . .	37.5	15.8	18.9
10/20 Non-protein nitrogen . . .	41.9	33.6	
Urea nitrogen . . .	16.9	14.3	
10/29 Non-protein nitrogen . . .	33.6		
1937.			
4/16 Non-protein nitrogen	30.0
Urea nitrogen	15.5

TABLE 6.—URINARY CHLORIDES AND URINARY VOLUMES.

Date, 1936.	Urinary chlorides (in milligrams as chlorides).			Urinary volumes (in cubic centimeters).		
	M.H.S.	J.B.L.	J.C.L.	M.H.S.	J.B.L.	J.C.L.
8/30 . . .	6,062.5	5,883	..	970	2,220	
8/31 . . .	7,047	5,772	..	870	2,220	
9/1 . . .	10,400	4,346	..	1,225	2,430	
9/2 . . .	4,320	3,350	4,220	800	2,795	1,190
9/3 . . .	1,010	1,180	1,250	720	2,960	1,780
9/4 . . .	384	264	306	590	1,760	3,060
9/5 . . .	19	13	25	640	2,590	2,000
9/7 . . .	4	6	11	550	2,460	1,520

There was a steady decrease in the urinary excretion of chlorides beginning on the first day. On the last day a few milligrams only were found in the urine (Table 6). These findings confirm

McCanee's⁶ work. The rise of chloride excretion in one subject, M. H. S., on the last day of his control period was due to increased salt intake on the preceding day following the playing of 3 sets of tennis.

None of the subjects had any notable symptoms until the fourth day of the experimental period. At that time, all 3 had occasional vague muscular cramps and a sense of fatigue. Temporary weakness was felt following the radiant-heat baths. One of the subjects had an indefinite sensation of epigastric discomfort; 2 had eructations and flatus. None of the subjects had pronounced loss of the sense of taste except for vegetables and salt-free bread during the last 2 days, possibly because the salt deficiency was not carried to the extreme degree of McCanee's⁶ experiments or because of the attractiveness of the food served. Thirst was noted by all and was not relieved by distilled water. The subject who had the highest urea nitrogen and non-protein nitrogen determinations noticed a dry mouth despite a high fluid intake; also a peculiar taste which was probably due to the excretion of urea in the saliva. All subjects lost weight in amounts varying from 4 to 10 pounds which was regained within 24 hours after the beginning of the recovery period. There was increasing lassitude and desire to sleep during the day. The inability to sleep well at night was probably due to the temperature of the control room. Approximately 30 gm. of salt and large amounts of water were ingested in the first 2 days following the experiment. All 3 subjects developed a marked edema, similar to that seen in acute nephritis. One subject increased in weight by 14 pounds in 24 hours.

Comment. The fact that no significant change occurred in the secretion of hydrochloric acid by the stomach in spite of marked sodium chloride deficiency has a simple explanation. It must be remembered that in the absence of diarrhea, the bowel excretes but a small amount of chloride. This means that most of the chlorides secreted by the stomach must be resorbed lower in the gastrointestinal tract. Thus there would be no advantage to the body economy to suppress secretion of hydrochloric acid in the stomach. The chlorides excreted through the bowel comprise but a small fraction of the chlorides ingested in even a very low salt diet. McCanee⁶ reported a loss of less than 100 mg. of chloride daily in the feces.

Under normal conditions, the kidneys and sweat glands excrete most of the excess sodium chloride from the body, while only a small amount is excreted through the bowel. McCanee⁶ showed that when the sodium chloride intake is restricted, the kidneys soon cease to excrete chloride in the urine, that excretion through the bowel is decreased, but that the skin continues to excrete a large amount of sodium chloride until the deficiency becomes extreme.

Consequently, in human subjects measures which increase sweating and decrease intake of sodium chloride are the only ones available to induce salt deficiency in the body. In animals, it is possible to drain the stomach continually by the method of Dragstedt and Ellis,² but this is not practicable in human subjects, and furthermore is not a physiologic means of salt excretion.

The appearance of edema during the period of recovery is not an evidence of a severe degree of sodium chloride deficiency. Baird and Haldane¹ and Torbert and Cheney¹⁰ have reported this effect following the ingestion of large amounts of salt by normal people. As might be expected, the edema in the subjects of our experiment was much more marked than that described by these authors. The explanation of this phenomenon is the deposition of water with the excess sodium chloride in the intercellular spaces. Probably the same mechanism causes the edema which appears in chronic nephritics when sodium chloride is added to a previous low salt diet.

The purpose of our work was to determine whether or not loss of chlorides through the sweat causes a decrease in gastric acidity. Since in normal subjects no significant decrease in gastric acidity was found, it is unlikely that loss of chlorides causes the anacidity found in some patients with exophthalmic goiter or with anxiety states complicated by the hyperventilation syndrome.

Summary. Three normal human males were subjected to a state of sodium chloride deficiency by decreasing the sodium chloride in the diet and increasing the excretion of sodium chloride by sweating. The fall in urinary and whole blood chlorides, the rise in urea nitrogen and non-protein nitrogen in 1 of the subjects, and the symptoms which appeared, indicated that a state of sodium chloride deficiency had been established. Deficiency of sodium chloride produced no significant changes in the gastric secretion of either free or total hydrochloric acid in the 3 human subjects studied.

Grateful acknowledgment is due to Josephine Dickison, A.B., A.M., and Florence Selvin, A.B., for the blood and urine chloride determinations made for this study; to Miss Ramona Greefken for the gastric analyses; to Rosalie C. Silverberg, A.B., for the chloride analyses of the bread and butter, to Eunice Barg, A.B., for the preparation of the diets, and to the physiotherapists for supervising the radiant-heat baths.

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THE ORIGIN OF EMOTIONAL FACTORS IN NORMAL PREGNANT WOMEN.

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THE present study is based on Streecker's¹ recent paper which presents a new thought in obstetric care. The maternity hospital utilized was the Preston Retreat, presenting an ideal service for this particular kind of study, because of the careful economic and social investigation of each family in their home, and direct supervision of each patient by the chief of service in the outpatient clinic as well as in the wards. The material was only 100 cases, of which 50 were adequately followed up, but a report of this small number is justified on the basis of sufficiently definite conclusions. The largest percentage of our patients were of Irish descent, constituting 60 of the group; there were 25 Italians, 10 of German descent, 2 Jewish, and the remaining 3 were of mixed origin. We have no colored patients in the Preston Retreat.

By "normal pregnant women" we mean registered prenatal patients without obvious disease, or the average mother from the point of view of any maternity department in any hospital, since the job is of necessity one of obstetrics. The routine of prenatal, natal, and postnatal care had doubtlessly been carried on with efficiency, yet we are forced to conclude from our study that a few of the so-called normal patients must have been potentially psychotic, and that a majority of them had specialized anxieties relating to pregnancy. It is likely therefore that in any hospital where the service is too large for the chief to have any routine contact with the patient, the possibility of emotional problems, so serious that they might result in puerperal psychoses, might be overlooked, underestimated, or disregarded.

It was the examiner's idea to create a rapport necessary to gain the confidence of the patient for the simple matter of getting facts rather than to establish any sort of transference necessary in dealing with neurotic patients. Sufficient time was given to allow the patients to speak without feeling hurried. An attempt was made to individualize each patient and conduct the interview in relation to the type of person presented. In the event that there seemed more to say than the information we were trying to secure, the patient was seen again and added data secured with as little direction as possible. Sympathy and interest was the rule since we had no idea

of including any psychiatric procedure in our clinic, intending to refer all cases calling for psychiatric therapy.

Our material was taken from a non-selected group and we feel that it represents a satisfactory cross-section of the whole. Of the 100 patients, 50 were adequately followed up after the birth of the infant to determine what measure of adjustment was made and to be used as a comparison between the pregnant woman and the non-pregnant. By an overwhelming majority our patients frankly confessed more anxiety during the period of pregnancy than previously, which was to be expected inasmuch as these women, belonging to a low level in the economic group, reflected anxieties largely related to poverty. From this it may be deduced that most women are more anxious during the period of pregnancy and that the type of anxiety is chiefly conditioned by the economic and social group from which they are drawn.

We present the physical factors associated with this group with the idea that associated complications, though mild, might play a part in influencing states of anxiety. There were in all, syphilis, 2 cases; malnutrition (slight), 10; moderate anemia, 2; pernicious-like anemia (due to pregnancy), 1; mild toxemia of pregnancy, 3; functional heart trouble, 3; organic heart disease, 1; vaginitis, 1; carious teeth, 20; and oral sepsis, 1. Except possibly for the 2 instances of lues, we feel that the physical factors were irrelevant to anxiety states of this group.

Since economic factors seemed to play such an important part in conditioning the anxiety of these patients, a short summary of the social-economic picture should be presented. Of these 100 women, 40 had never been pregnant before, 32 were pregnant for the second time, and 28 a third time or over. It was interesting to notice that we had no cases of nausea of the type that might be attributed to psychic rejection of the child. Of the 40 women pregnant for the first time, only 2 rejected the idea of having their infants, the reasons stated were: (1), economic reasons, 1; (2), separated family, 1. In the second group of 3 women each having had 1 child, 3 rejected the idea of having another baby; the reasons for not wanting: (1), economic stress, 2; (2), father serving jail sentence, 1. In the third group of 28 women 12 rejected the idea of having another baby; the reasons for not wanting: (1), economic factors, 10; (2), separation from husband, 1; (3), chronic illness of husband, 1.

It is remarkable that only 17 out of 100 women in adverse circumstances resented their conceptions, since all were aware that economic insecurity was definitely exaggerated by pregnancy. Of the 100 cases, 20 were on relief, 30 had government jobs, and 50 varied temporary work. The average allowance for a family of 3 on relief was \$10.20 a week, with an added dollar for each extra child. The average allowance for those who had government positions was \$15.00 a week regardless of the size of the family. Various other

miscellaneous jobs averaged \$18.00 a week, regardless of size of family.

We have divided our cases into four groups: *a*, good; *b*, temporarily adequate; *c*, fair; *d*, poor; interpreted as follows: by "good" we refer to the type of family where both economic considerations and types of parents promise a satisfactory way of living and an intelligent adjustment to the whole situation. This group, which should improve their general status when the abnormal economic slump has passed, numbered 25. By "temporarily adequate" we indicated families who were under great economic strain but managing well nevertheless, numbering 17. By "fair" we mean families whose funds were inadequate and whose prospects of improved conditions extremely doubtful, of whom there were 25. By "poor" we refer to the families who because of stupidity, ill health and general maladjustment suggest that any improvement would be absolutely impossible, amounting to 33.

Among the 75 women who freely admitted more anxiety during the period of pregnancy, an increase in the degree of anxiety was noted in those women who had 2 or more children. But it appeared that the economic-social situation did not quite account for the whole of this exaggerated anxiety, and in future studies we would like to consider the possibility of some physiologic reason for those women having 2 or more children to be markedly more nervous. Of the total 100, only 3 stated that they were less anxious during pregnancy and 22 said that they felt "about the same."

The specialized types of anxieties were divided into four groups: 1, anxiety relating to economic security, 75%; 2, phobias, 16%; of these 12 expressed fear of death, 2 were concerned with "old wives tales," relating to the child being marked, and 2 had serious phobias concerning their own health; 3, anxieties relating to husband, 7%, of whom 2 were worried about their looks being spoiled, 2 were suffering from the knowledge of infidelity, 2 were deserted by their husbands, and 1 whose husband was serving a prison term; 4, anxiety relating to other members of the family, 10%; of these all were living with their in-laws and felt that there was too much interference. In our total group, there were 3 women who showed marked depression but their situation seemed to justify the state of mind, so were not included in the potential psychotic group noted below. There were only 3 patients who gave histories of previous nervous breakdowns.

Finally, we come to the potentially psychotic mothers. Three of our patients furnish us with an excellent example of why emotional factors in pregnant women should be considered with a full sense of responsibility. We feel these cases important enough to consider somewhat in detail.

Case Reports. CASE 1.—Mrs. H., aged 24, unfortunately did not come under our prenatal observation as a case for special attention since our

neurologic interests had not been aroused at the apparent time of her emotional upset. The word "apparent" is an important item in realizing that a superficial interest in the social and economic set-up, and ordinary routine obstetrical examination is *not sufficient* to detect the subtle processes of possible mental disorder. Therefore our initial knowledge of Mrs. H.'s emotional difficulties occurred when her infant was 6 months old. Although she seemed a well poised, quiet woman, subsequent history taking disclosed the fact that she had "attacks" off and on for many years, culminating in a maniacal state in which she tried to stab her husband with a carving knife. This is her first child, and her background is one of having been sent by her father to live with a foster mother at her mother's death. Mr. H. is out of work, receives \$10.20 weekly relief money, is fond of his wife, but is a thoroughly inadequate personality who compensates by bragging. Mrs. H. claims to love her husband, but all of her violent attacks are directed against him. The present period of the wife's mania dates from the time that the husband lost his job and stayed home all of the time. In the absence of physical pathology, we sent this woman to a psychiatric clinic for diagnosis and treatment, delayed by poor patient coöperation.

CASE 2.—Mrs. M., white, aged 23. Second pregnancy, one living child, a girl of 3. During the seventh month of her pregnancy she confessed that if she had a male child she seriously did not know what she would do about it, stating that she had a marked loathing for the male genitalia. We did not refer her to a psychiatric clinic but decided to wait until the infant was born and observe whether or not there would be some sort of spontaneous adjustment in the event of a male child. It was a male child, but the mother seemed fond of her infant and nursed him. Nevertheless, on account of the prior obsession, discovered only after special questioning, we are going to follow up her emotional reactions in the postnatal clinic and refer her in the event that it seems necessary, since no physical complications exist.

CASE 3.—Mrs. J. M., white, aged 24, had no previous history of emotional upset. Home situation moderately good. In the eighth month of her pregnancy she stated that she had marked phobias concerning the event of childbirth, believing that "something terrible was going to happen." She had insomnia and marked tremors of her hands and legs. During the ninth month of her pregnancy the nervousness seemed somewhat better, but greatly increased by the birth of a deformed infant showing congenital absence of the abdominal wall followed by death on the third day. Mrs. J. M. now believes that she had special knowledge of the event before it happened, and that her intuitive feelings about things will predestinate their occurrence. We will observe her carefully and refer her to psychiatric clinic at a later date if she does not get rid of this delusion.

Conclusions. 1. So-called "normal pregnant women" might well be highly abnormal, and even if they are not they are anxious to a degree beyond that of the so-called "normal" non-pregnant female.

2. Types of anxiety are influenced by the social and economic group from which they are selected.

3. In the group of 50 cases adequately followed up after childbirth, even though the economic situation was unchanged, there was a definite lessening of anxiety in 40 cases.

4. We make a plea for at least one experienced "dispensary" staff attendant at each prenatal clinic, and for a note of the nervous status on each obstetrical record.

5. All women showing phobias or even marked anxiety during

pregnancy should receive sympathetic encouragement by the chief of service, and if necessary, psychiatric advice.

6. Among 100 presumably normal pregnant women 75% showed anxiety related to economic stress; 7% to their husbands, 10% to other members of their families; while 16% showed definite phobias concerned with fear of ill-health or death, or of the child being defective.

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PNEUMOCOCCUS MENINGITIS WITH RECOVERY.

A REPORT OF THREE CASES.

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RECOVERY from pneumococcus meningitis is a very rare occurrence. Since Bedell's cases (3) in 1934, occasional reports are found in the literature; but several of these are not proven cases of pneumococcus infection, from the laboratory evidence presented. The use of sulphanilamide has been advocated in certain pneumococcal infections. The gratifying results obtained in these cases suggests the efficacy of this drug in the treatment of such cases and has prompted us to report the 3 cases in detail.

Case Reports. CASE 1.—J. H. C., Jr., a student, aged 16, was admitted to this hospital under the care of one of us (W. B. A.), on the evening of July 23, 1937. The complaint at that time was of headache and fever. The family history was quite irrelevant. The past history was strikingly negative except for the usual childhood diseases and a tonsillectomy in 1935.

He was in excellent health until June 14, 1937, when he was in an automobile accident and was thrown clear of the car. This resulted in the fracture of his skull and right clavicle. He was unconscious for $1\frac{1}{2}$ hours and was irrational for the 3 days after the accident. The fracture of the skull was in the right frontal region, involved the right frontal sinus and extended into the ethmoid sinuses at the base of the skull. From the onset, the vision in the right eye was greatly impaired, and this was thought to be due to the trauma. Convalescence seemed to be entirely satisfactory until July 6, 1937, when he developed a fever of 103° F. with chest pain and an unproductive cough. These symptoms were diagnosed as pneu-

monia and after a few days he became afebrile. However, on July 21, he again had a sudden rise in temperature to over 103° F., with a subsequent continuous fever ranging between 103° and 104° F. On July 22, he developed a stiff neck and became stuporous, and with this, vomiting was almost constant.

Examination. The boy was acutely ill, semicomatose, irritable and had obviously lost weight. The temperature was 104° F., pulse 132 per minute and the respirations were 24 per minute. The face was flushed. The skin was warm and dry, and no petechiæ or purpuric areas were seen. There was no edema. There was a small scar just below the left eyebrow which had the appearance of having been recently acquired. There were no gross skeletal abnormalities. The eyes were of interest: they were not prominent; the extra ocular movements were fairly well performed—save for inability to converge with the right eye; the conjunctivæ were injected. The right pupil was larger than the left and gave a paradoxical response to light. The left pupil reacted promptly to light and the right pupil gave a consensual response. The ocular fundi, save for rather pronounced pallor of the right disc, were thought to be normal. The ear drums were intact and there was no evidence of infection. There was a slight mucoid discharge from the nose. The pharynx was not remarkable. There was no glandular enlargement of note. The lungs were quite clear to percussion and auscultation. The heart was not enlarged and except for the tachycardia was considered normal. The blood pressure was 108/68. The abdomen was flat and no viscera or masses were palpable. The genitalia were of normal configuration and the rectal examination was not remarkable.

Examination of the central nervous system revealed that the cranial nerves were intact with exception of partial impairment of the optic nerve on the right. No motor or sensory changes were discovered, except for general hyperesthesia. The deep reflexes were present and very active. The superficial reflexes were normal in response and there were no abnormal reflexes elicited. There was marked stiffness of the neck with positive Brudzinski and Kernig signs.

The blood count showed: Hemoglobin, 13 gm. (90%); erythrocytes, 4,830,000; leukocytes, 36,500 with adult and juvenile neutrophils forming 90% of the total count. The blood Wassermann reaction was negative. The urine was acid with a specific gravity of 1.022. There was but a slight trace of albumin and no sugar was present. No formed elements were present. The urine culture was sterile. The blood chemistry revealed a fasting sugar of 91 mg. %; and non-protein nitrogen of 20 mg. %.

Roentgen ray examination of the chest showed the lungs to be clear; those of the head revealed evidences of an old fracture in the right frontal region involving the right frontal sinus and extending to the base of the skull; those of the sinuses showed an old fracture of the right frontal bone which extended into the right frontal sinus, and clouding of the right ethmoids and right antrum; those of the orbits did not reveal any evidence of osteomyelitis.

The blood cultures were sterile.

The first specimen of cerebrospinal fluid was obtained under an increased pressure and the Queckenstedt was negative. The fluid was opalescent and contained 22,500 cells per c.mm. The differential count showed 93% neutrophils and 7% lymphocytes. The stained smear showed a few organisms and the morphology of these suggested pneumococci. The cultures revealed a bile-soluble organism identified as a pneumococcus (Type XIV).

Treatment. It was thought advisable to institute drainage by repeated lumbar punctures. However, with the striking improvement in the patient's condition within the first 36 hours, this procedure was only done to deter-

mine the cell count and obtain cultures. It was not necessary to do a lumbar puncture to relieve the symptoms of pressure at any time after the first 36 hours. When the causal organism was definitely identified, sulph-anilamide therapy was begun immediately. During the first 24 hours he received 2.4 gm. of the drug by mouth. During the subsequent 4 days he received 4.8 gm. by mouth per day. On the fifth day this was increased to 5 gm. in the 24 hours and in the following 24 hours he received 6 gm. of sulph-anilamide by mouth. Finally on the ninth day of hospitalization, or the eleventh day of the acute illness, the drug was stopped after the patient had received 3 gm. and no further therapy was employed.

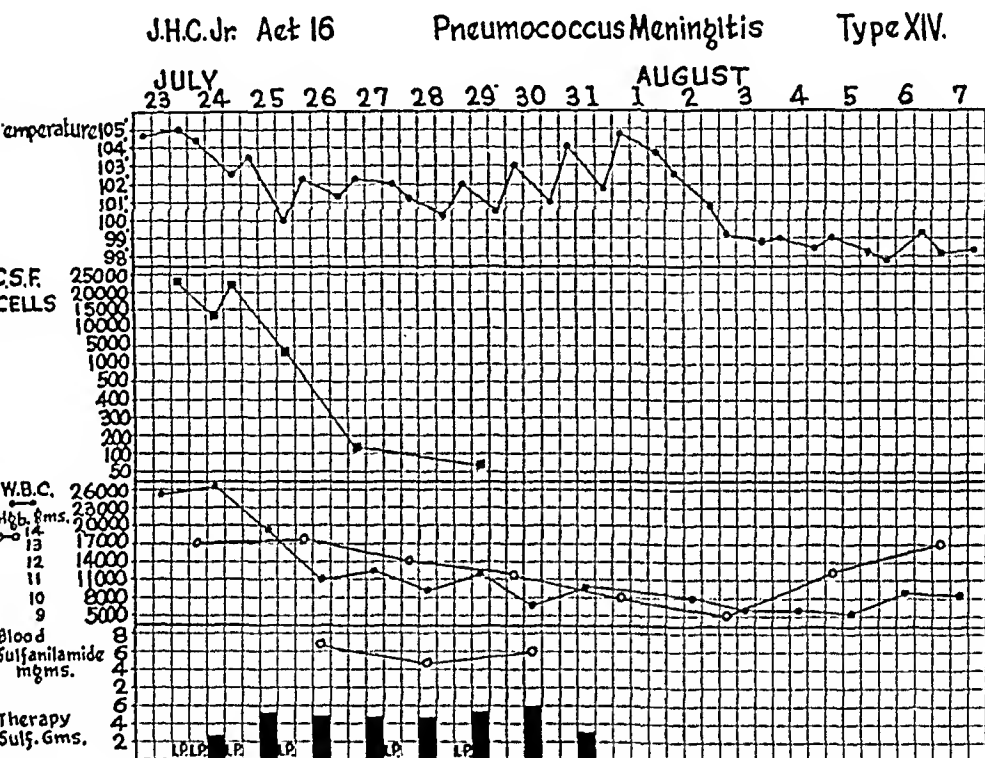


CHART 1.—Case 1. J. H. C., Jr., male, aged 16, meningitis due to pneumococcus Type XIV.

Course. The temperature continued high for the first 36 hours after admission and gradually fell but did not become normal. After the third day of sulph-anilamide therapy the temperature gradually rose until it reached 105° F. by the eighth day of treatment. We felt that, with the clinical improvement, we were justified in assuming that the elevation in temperature was due to the drug used; therefore, the administration of sulph-anilamide was discontinued. It was gratifying to find that the temperature fell rapidly to normal in the next 24 to 36 hours and remained so during the remainder of the patient's hospital stay. It is of interest that sulph-anilamide had no deleterious effects on the cells of the blood.

The cerebrospinal fluid cell count was high on the first 3 occasions and it fell rapidly. With the fall in this cell count there was a gradual change noted in the types of the cells. At first, practically all were neutrophils and latterly the mononuclear elements predominate. The organisms were scanty in the bacterial smears. The number of organisms on culture was not abundant, and the culture taken 48 hours after admission was sterile.

The subsequent cultures were likewise sterile. Sulphanilamide had been given over a period of some 36 hours before the first sterile culture was obtained. The blood sulphanilamide level at this time was 6.7 mg. per 100 cc. of blood. Unfortunately, we do not know the sulphanilamide level in the spinal fluid as such determinations were not being done at that time.

The improvement in the patient was most dramatic; the pertinent data are collected in the appended chart.

A very curious and perplexing feature occurred on the day after admission when the left upper eyelid was found to be edematous. The edema became more marked and a definite swelling was noted in the periorbital tissues, resulting in slight proptosis of that eye. It was our feeling that he probably had a periorbital abscess. This was treated with hot compresses and with the general improvement in the patient the swelling subsided, so that no surgical intervention was necessary. At the time of discharge there was no residuum of this swelling.

In a recent communication from the patient he states that he is feeling very well, has gained weight and is not experiencing any untoward effects from his illness.

CASE 2.—F. T., a salesman, aged 42, was admitted to this hospital under the care of Dr. Walter Dandy, on December 20, 1937. The complaint was severe occipital headache, and he was seen by one of us (W. B. A.) at Dr. Dandy's request.

The history is very interesting and dates back to early in 1935. The patient's first complaint was progressive deafness with tinnitus in the right ear and a unilateral headache on that side. There was no associated vertigo or vomiting. For these complaints he was admitted to the neuro-surgical service on April 26, 1937. The findings were essentially negative but the audiometer tests pointed to an acoustic nerve tumor on the right side.

On April 27, 1937, a neurinoma weighing 10.5 gm. was removed. The subsequent postoperative course was very satisfactory so that on May 7 a spino-facial anastomosis was done. Dr. Dandy described a leak of clear cerebrospinal fluid that filled the wound several times and no site for the leak was found. Following this operation the patient had a moderate rhinorrhea. The wound was again explored on May 17, and in Dr. Dandy's words: "The rhinorrhea in this case is most unusual. It must come from the operative field because there never has been any before The wound was opened partially and the angle was thoroughly inspected. It was perfectly clear. There was no hematoma and the defect looked about as it did at the time of operation. We tried to place a piece of muscle in the porus acusticus, but it would not stick and wax would not stick either." Repeated efforts were made to scarify and obstruct the right Eustachian tube without any satisfactory result.

The rhinorrhea persisted and further efforts were made by Dr. S. J. Crowe and Dr. J. W. Baylor to occlude the right Eustachian tube by the local application of iodine. These attempts again proved unsuccessful. The rhinorrhea persisted and the patient was quite well until December 15, 1937. On this day, 1 hour after eating, he vomited and later developed a severe occipital headache. No bulging was noticed in the right cerebellar defect, nor was there any increase in the amount of cerebrospinal fluid discharge from the nose. After 24 hours the patient's neck became stiff and he developed a febrile reaction, the temperature rising on occasions to 103° F. He did not become delirious, lose consciousness or have convulsions. He was again admitted to Dr. Dandy's service with a temperature of 99.6° F., pulse of 86 and respirations of 14, on December 21.

Examination. The examination at the time of admission revealed a well-nourished man, who was very drowsy and who complained constantly of a severe occipital headache. There was no petechiæ. The skin was

warm and moist. The ocular fundi were quite normal. The rhinorrhea was noted, but it was no more marked than on the previous examinations. The lungs were quite clear. The cardiovascular system showed no abnormalities. The blood pressure was 132/68. The neurologic examination revealed a very marked stiff neck and a bilaterally positive Kernig. The defect in the cerebellar region was quite soft. There was a palsy of the seventh cranial nerve on the right, which was of the peripheral type, and the nerve had shown a marked return of function after the spinofacial anastomosis. The fifth cranial nerve was intact. There was no nystagmus, ataxia or staggering and the Romberg sign was negative.

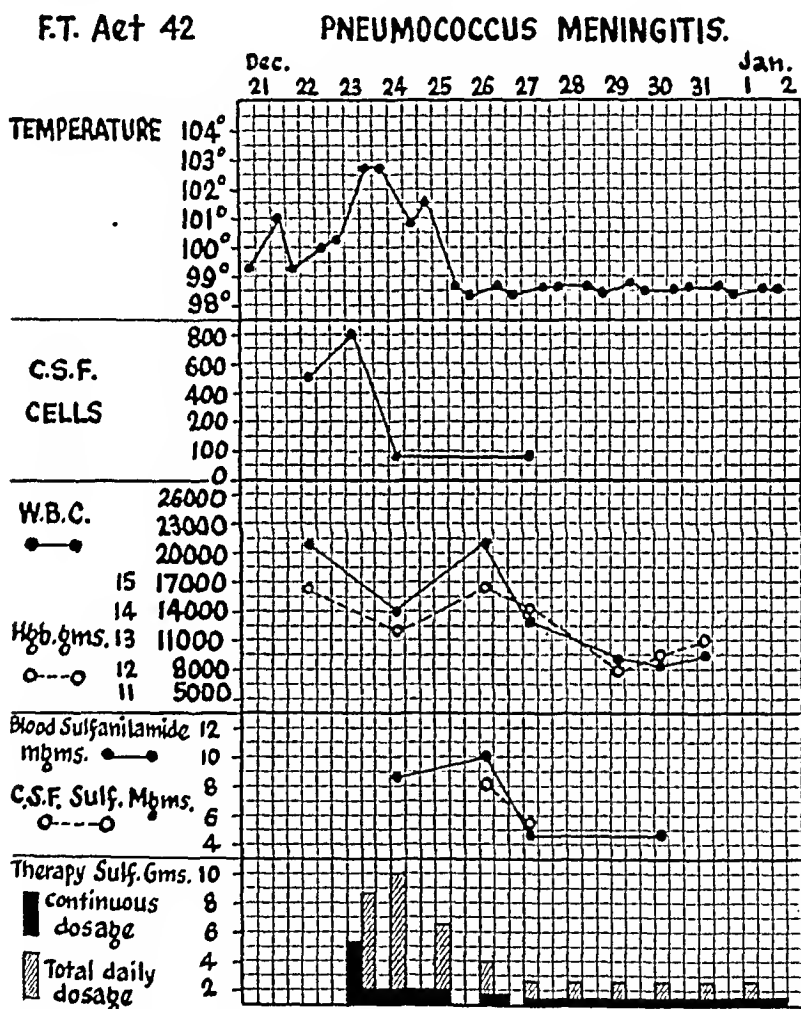


CHART 2.—Case 2. F. T., male, aged 42, meningitis due to pneumococcus Type XXIX.

It was felt that the patient had a meningitis due to a retrograde infection by way of the Eustachian tube, middle ear and mastoid cells:

The blood count showed: Hemoglobin, 102% and leukocytes 20,150 with a normal differential formula.

The urine was normal in every respect. The blood Wassermann reaction was negative. The blood cultures were sterile.

The first specimen of cerebrospinal fluid was obtained without any

increase in pressure and the Quekenstedt was negative. The fluid was opalescent and contained 500 cells, all of which were neutrophils. The stained smear did not reveal any organisms but the culture revealed a bile-soluble organism identified as a pneumococcus (Type XXIX).

Treatment. The treatment in this case was not directed at repeated lumbar puncture as there was no obvious increase in intracranial pressure. Because of the success attributed to sulphanilamide in Case 1, this was instituted on December 23 after the organism had been accurately identified. The patient received sulphanilamide by mouth only. He was given 5.3 gm. of sulphanilamide with sodium bicarbonate on the morning of December 23 and received 1.5 gm. every 4 hours during the remainder of that day and the following day. Through the day of December 25 he received 0.9 gm. every 4 hours, and from December 26 to January 2, 1938, he was given 0.6 gm. of sulphanilamide 4 times a day. Unfortunately, through some misunderstanding the sulphanilamide was discontinued through the nights of December 25 and 26 and we feel that this explains the low blood and cerebrospinal sulphanilamide levels on the morning of December 27.

Course. The day after treatment was instituted the patient's condition had improved. The headache was much less severe and had entirely disappeared by December 27. During the first 48 hours after treatment was commenced the rigidity of the neck became less and was entirely absent by December 26.

The temperature fall was dramatic as seen in Chart 2.

As in Case 1 no deleterious effects from the therapy were noted on the blood picture.

The culture of the spinal fluid was positive for Type XXIX pneumococcus before treatment and on the afternoon of the institution of therapy was still positive for the same organism. The subsequent cultures were sterile and the cell count fell from an original level of 500 to 80 cells.

It is very common to find cyanosis of varying intensity in individuals receiving sulphanilamide. The cyanosis in this case became marked, but in spite of continuing sulphanilamide it had entirely disappeared on December 31 (eighth day of therapy).

The patient was discharged on January 2 entirely recovered from the meningitis. At the time of writing he is in this hospital and Dr. Dandy has repaired the defect in the dura causing the leak, with gratifying results.

CASE 3.—V. L. R., an 18-year-old negro, was admitted to Dr. W. T. Longcope's service of this hospital, on December 24, 1937, because of headache, fever and delirium of 3 days' duration.

The family history was irrelevant.

The past history was non-contributory, save for infrequent mild headaches several years previously. There had been no other symptoms of sinusitis, and no more than the usual one or two colds a year.

The present illness began 6 days before admission when the patient complained of frontal headache. There had been no previous upper respiratory infection. The headaches gradually became more severe, and 3 days before admission he began to feel feverish and developed a slight cough. There was occasional vomiting. He was delirious at times. There was an indefinite story of slight puffiness of the eyelids.

Examination. The patient was a well-nourished and well-developed young negro. He was restless and delirious. The temperature was 104° F., the pulse 112 and the respirations 32. The skin was hot and dry. No rash was seen. The right pupil was small, the left large; both reacted well to light. The fundi were normal. The ear drums were normal. No sinus or mastoid tenderness could be elicited. The tonsils were of moderate size. The pharynx was moderately injected, and there was a purulent postnasal

discharge. The lungs were clear, and the heart was not enlarged. The blood pressure was 120/70. The examination of the abdomen and genitalia was not remarkable. The deep reflexes could not be obtained. No abnormal reflexes were elicited. The cranial nerves were intact, and there were no gross motor or sensory changes. There was marked stiffness of the neck, and a positive Kernig sign.

The blood count showed: Hemoglobin, 13.8 gm. (94%); erythrocytes, 4,300,000; leukocytes, 12,300 with 90% neutrophils. The blood Wassermann reaction was negative. The urine was normal. The blood cultures, taken on the first and second days, were sterile.

Lumbar puncture revealed cloudy spinal fluid under a pressure of over 55 mm. of water. There was a normal jugular response. The cell count was 8000 per c.mm., with 70% neutrophils. The stained smear showed no organisms, and the patient was therefore given 10 cc. of the concentrated New York State antimeningococcus serum, intrathecally.

Sulphanilamide was begun, the dosage varying between 6 and 8 gm. a day. It was given subcutaneously in the form of an 0.8% solution with 1/6 molar sodium lactate, or by stomach tube with sodium bicarbonate.

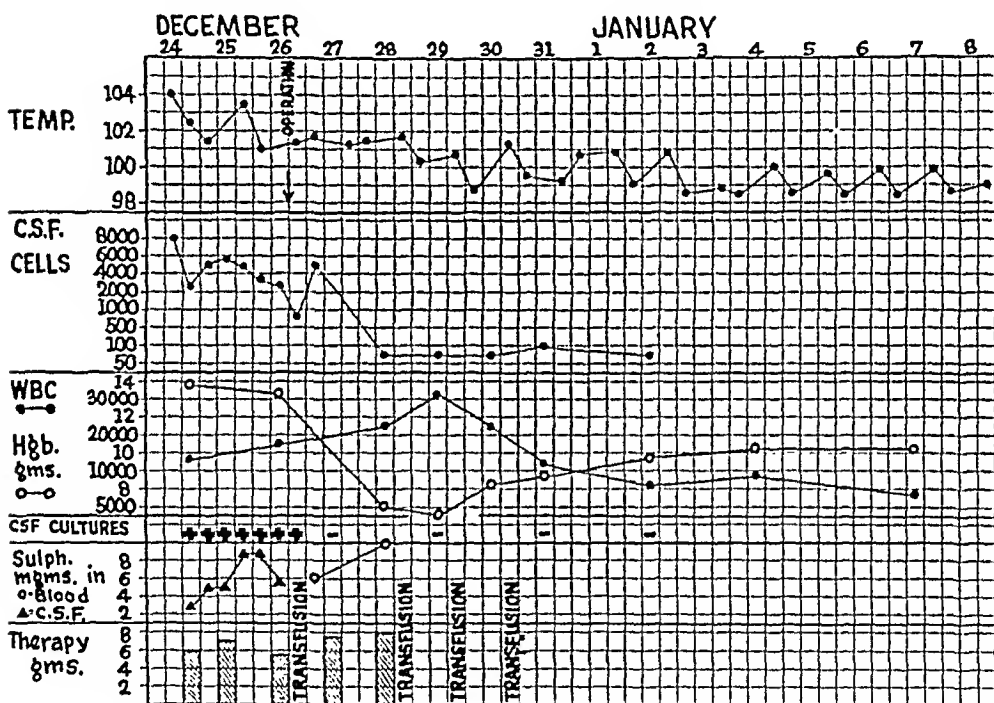


CHART 3.—Case 3. V. L. R., colored male, aged 18, meningitis due to pneumococcus Type XX.

Course. Lumbar punctures were done every 8 hours. Culture of the fluid obtained at the first 7 punctures all showed pneumococcus Type XX. At the second and third punctures antimeningococcus serum was given. After the nature of the organism was determined this was discontinued, and 10 cc. of 1% sulphanilamide was given, intrathecally, following drainage of the spinal fluid.

On the second hospital day his clinical condition was worse. He was extremely restless and combative. There was a divergent strabismus. The heart had apparently dilated, for the apical impulse had shifted to the anterior axillary line. There was a marked dirotic wave in the pulse.

The blood pressure remained at 120/70. The spinal fluid sulphanilamide levels were 4.9, 4.8 and 8.4 mg. %.

On the third day the clinical condition was unchanged, save that the blood pressure had fallen to 90/50. Large amounts of sedatives were required to control the restlessness. The temperature had varied between 101° and 103.6° F. The hemoglobin was 90%. The leukocyte count had risen to 17,100. The spinal fluid cell counts were 3500 and 2500, with spinal fluid sulphanilamide levels at 8.5 and 5.6 mg. %. Cultures remained positive for pneumococcus Type XX. Sinus Roentgen rays were taken but were unsatisfactory, because it was impossible to hold the patient's head sufficiently still. Examination with a nasopharyngoscope, however, showed a purulent discharge coming from the orifice of the left frontal sinus.

Because there was no evidence of any other focus, a radical frontal operation under ether anesthesia was performed on the third hospital day by Dr. Samuel Crowe. A large quantity of pus was evacuated from both frontal sinuses. There was considerable erosion of bone in the anterior walls of the frontal sinuses, but no evidence of communication with the meninges through the posterior walls was found. Cultures of the pus from the sinuses showed pneumococcus Type XX.

Following operation the blood pressure fell to 82/44, and he was given a transfusion of 600 cc. and intravenous normal saline. On the following day (the fourth) his clinical condition was unchanged. The spinal fluid cell count was 5000, but the culture was sterile, as were all subsequent cultures and the 2 mice inoculated with the spinal fluid intraperitoneally survived. The blood sulphanilamide was only 5.9 mg. % and it was felt that the sulphanilamide given by stomach tube was probably not being adequately absorbed, so the subcutaneous method only was used thereafter. The urine on this day showed a trace of bile and a moderate amount of urobilin. The sclerae were faintly icteric.

On the fifth day the blood sulphanilamide level had arisen to 10.7 mg. %. The hemoglobin had fallen to 48%, and the leukocyte count had risen to 22,000. The urine contained a large amount of urobilin. Sulphanilamide was therefore discontinued, and the patient given a transfusion of 600 cc.

There was evidence of some clinical improvement. The left border of the heart had returned to its former position, 8 cm. to the left of the mid-sternal line. The blood pressure has risen to 120/70, and the dicrotic wave in the pulse had disappeared. At times, the patient would respond slightly to commands. There was, however, some blurring of the nasal margins of the optic discs.

Several attempts at lumbar puncture were unsatisfactory, because of the extreme restlessness of the patient despite large amounts of sedatives. Because it was deemed imperative to determine whether or not a block had occurred, a 16-gauge needle was inserted in the lumbar region under ether anesthesia. Following bilateral jugular compression 300 cc. of almost clear fluid was obtained. The cell count was only 80. The needle was then filed off 1 cm. from the skin and left in place.

On the sixth day he was much improved, and able to take fluids by mouth. Spinal fluid was draining freely from the needle. The hemoglobin was 40%, the leukocyte count 32,000 and the serum bilirubin 3 mg. %. He was given a third transfusion.

Following this he continued to improve rapidly. On the eighth day the spinal needle was removed. The cell count had remained between 80 and 100 cells, 70% of which were neutrophils. The hemoglobin had risen to 68%. The leukocyte count had fallen to 12,300, and several nucleated red cells and 5.3% reticulocytes were present in the blood smear. Urobilin had disappeared from the urine. The operative wound was remarkably clean, but some purulent discharge continued to be present in the nasopharynx.

TABLE 1.—OTHER CASES OF PNEUMOCOCCIC MENINGITIS REPORTED SINCE 1934.

Ref. No.	Sex.	Age.	Onset.	Cell count of original cerebro-spinal fluid.	Identification of organism.	Treatment.
1	F	9	Two days following pneumonia	1600 per c.mm.; mostly polys.	No organism seen in smear or culture	None.
2	F	9	Otitis media; chronic mastoiditis	2000 per c.mm.	Pneumococcus Type V	Antimeningococcus serum; transfusion; sulphanilamide—intraven., intraspinal, intramus., subcutan.
3	F	42	Four days after onset of acute sinusitis	8000 per c.mm.; polys., 88%	Organism identified in smear and culture, pneumococcus Type IV	Continuous cisternal drainage and cisternal irrigations.
4	F	9	Otitis media with recrudescence	1686 per c.mm.; polys., 88% 2. 2050 per c.mm.	No organism in the smear or culture originally. Organisms in smear and culture Gram diplococci with capsules and in short chains; not typed	Spinal drainage; transfusions.
5	M	29	"Primary" ?	No statement	Cultures said to have confirmed	No treatment; ? "spontaneous."
6	F	25	Six days after tonsillectomy	540 per c.mm.; polys., 85%; lymphos., 15%	Organism in smear and culture; not typed	Antimeningococcus and antipneumococcus sera; mercurochrome by vein.
8	?	5	"Primary" ?	3500 per c.mm.	Gram diplococcus by smear and culture; short chain streptococcus	Cisternal drainage; antimeningococcus serum, small amount.
9	?	?	Mastoiditis	No details	Pneumococcus Type V	Prontylin—tabs. 1 g. 4 h. for 7 days—no effect, discontinued optochin was used throughout.
10*	?	?	After tonsillectomy and ethmoid op.	?	Stated Type XXXI	Sulphanilamide.
	?	?	48 hrs. after submucous resection and turbinate op.	?	Stated Type XXIX	Sulphanilamide.
	?	?	After double otitis media and double mastoiditis	?	Stated Type IV	Sulphanilamide.
11	M	59	Chronic otitis media and mastoiditis	18,600 per c.mm.; almost all polys.	Organism in smear and cultures; not typed	"Spontaneous;" symptomatic.
12	F	12 days	Organism in smear	"Spontaneous."
13	F	20	History of sinusitis; head injury	2420 per c.mm.	Organism in culture agglutinated in sera of Types I and II	Felton's serum by vein, cistern and subarachnoid space; glucose, 50%, by vein; MgSO ₄ , 33% by rectum.
14	F	43	Mild "cold" 2 weeks before	1060 per c.mm.; numerous erythrocytes	Organisms seen only in smears	Felton's serum, Types I and II.
15	F	7	7 wks. after a purulent otitis media	150 per c.mm.; polys., 80%	Pneumococcus Type III by culture	Spinal and cisternal drainage; antimeningococcus serum.
16	M	28	Head injury; C.S.F. from nose	Fluid cloudy—no cell count; polys., 100%	Pneumococcus Type I	Felton's serum—intrav. and intrasp.

* This and the 2 following cases are recovered ones from a group of 14 cases of pneumococcic meningitis.

On the elventh day his temperature had fallen to normal, and aside from the operative wound, he was apparently perfectly well. He was discharged on January 23, 1928, after 32 days in the hospital.

Discussion. Pneumococcus meningitis is a relatively uncommon disease. In a review of such cases reported since 1934 (Table 1) we are impressed with the fact that the meningitis is most commonly secondary to an otitis media or sinusitis. This does not seem unusual inasmuch as the upper respiratory tract is a common habitat for the pneumococcus.

Meningitis as a complication of lobar pneumonia would seem quite rare from our review of the reported cases. This is quite in keeping with the generally accepted statistics. In large series⁷ of cases of lobar pneumonia meningitis occurs as a complication in from 0.2 to 2.4% of all cases.

A striking feature in the tabulated cases from the literature is that the evidence in many is very inconclusive that the causal organism is the pneumococcus. This objection has been raised before. The organisms obtained in our 3 cases were identified in smears by Gram's stain. The cultures of the cerebrospinal fluid revealed typical bile-soluble organisms. The organisms were identified as Type XIV pneumococcus in Case 1; Type XXIX pneumococcus in Case 2; and Type XX pneumococcus in the last case. It seems beyond a doubt that we were dealing with pure pneumococcal infections. The organisms, in all 3 cases, though plentiful, were not found in overwhelming abundance in the spinal fluid.

The treatment in these cases was first directed at adequate drainage of the subarachnoid space. This played an appreciable rôle in the third case. A search for an apparent source of organisms in the mastoid and paranasal sinuses is of vital importance, and such a focus should be completely removed. It is apparent from Chart 3 and from the clinical description of that patient, that there was no improvement in the third case prior to the operation. Within 16 hours after the operation, however, the organisms had disappeared from the spinal fluid, and after 48 hours the spinal fluid cell count had dropped to 80, and clinical improvement had begun. Certainly the removal of the focus of infection which presumably was feeding organisms into the spinal fluid was a major factor in recovery in this case. No like focus could be identified in the first 2 cases, though it was strongly suspected in the first.

No toxic effects from the administration of the sulphanilamide were noticed in the first 2 cases other than moderate cyanosis in Case 2, and a moderate febrile reaction in Case 1.

The marked hemolytic anemia observed in the third case has been commented upon in other instances. It was quite severe in this case and it was necessary to give blood transfusions.

No specific antipneumococcus serum was used.

The sulphanilamide was given orally in all the cases and, in addi-

tion, it was given intrathecally and subcutaneously in the third case. Whether this patient would have survived without the additional use of sulphanilamide is a matter of conjecture. However, we feel reasonably certain that this drug was responsible for recovery in the first 2 cases. In 1 of the cases recently reported by Basman and Perley² a similar beneficial effect is shown.

Summary. Three cases of pneumococcus meningitis are reported. The organism was definitely a pneumococcus and the types were XIV, XXIX and XX respectively. The beneficial effects of sulphanilamide alone in Cases 1 and 2; and, with other procedures in Case 3, are demonstrated.

We are indebted to Dr. Perrin Long for his helpful guidance in the preparation of this report.

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BOOK REVIEWS AND NOTICES

TISSUE REACTIONS IN BONE AND DENTINE. A morphobiological study of the formation and the dissolving of bone and dentine. By ÅKE WILTON, M.D., Assistant Professor and Lecturer in Pathology at the Caroline Institute, Stockholm. Pp. 194; 64 illustrations and 5 plates in color. London: Henry Kimpton, 1937. Price, 15/.

THE book contains a summary of the results of the studies of the author on bone and dentine. In the first part the author discusses osteogenesis and dentinogenesis. The conclusion is drawn that the maturity of the matrix depends on the differentiation of the bone and dentine forming cells. Cells of low differentiation form but an immature matrix, which is transformed into mature matrix only after the cells have been fully differentiated. Though differentiation and proliferation usually appear to be antagonistic, under certain conditions as in rachitis or achondroplasia, a factor (N-factor) makes its appearance, which brings about an abnormally slow differentiation with a simultaneous decrease in proliferation (N-reaction).

In the second part of the book the author presents his findings on osteolysis and dentinolysis. He distinguishes: 1, active bone resorption occurring in young bone, which is characterized by unmasking and dedifferentiation of the osteocytes, which again proliferate and transform into other cells. This resorption has been observed by the author in experimental osteolysis by parathormone, Paget's disease, scurvy and osteogenesis imperfecta; 2, passive bone resorption, in older bone the osteocytes of which have lost the ability of dedifferentiation. This resorption is accomplished by reticuloendothelial cells; 3, lingering bone resorption which is interpreted as physiologic dedifferentiation of bone cells not accompanied by proliferation of osteocytes. The author believes that the alterations in scurvy and osteogenesis imperfecta are produced by a factor (W-factor) which brings about abnormal dedifferentiation with abnormal increase in growth (W-reaction). The N- and W- factors have, however, nothing to do with the real genesis of the diseases. Although the description and pictures given by the author did not convince the reader of the soundness of his deductions, the book certainly must be regarded as valuable and should be thoroughly studied by the student of bone diseases.

W. E.

CLINICAL URINALYSIS AND ITS INTERPRETATION. By ROBERT A. KILDUFFE, A.M., M.D., F.A.S.C.P., Director of Laboratories, Atlantic City Hospital; Pathologist, Atlantic County Hospital for Tuberculous Diseases, etc. Pp. 428; 40 illustrations. Philadelphia: F. A. Davis Co., 1937.

DR. KILDUFFE here brings out an easily readable book for the practitioner to use in his office, but insufficient in detail for the beginning medical student and too clinical in its interpretation for the laboratory technician. He enumerates and describes methods of distinct value that can be performed in a small office laboratory and discusses the interpretation of such examinations for the physician. He covers many tests in the book but does not specify the reaction, either physical or chemical, that makes the test possible. Even the busy practitioner in his leisure moments might like to know why certain reagents are needed in the performance of an analysis. An addition of this sort would not be too long. Many of the procedures give a presump-

tive result but when greater accuracy is needed additional tests are set forth. An excellent feature is the enumeration of certain fallacies that modify the interpretation of the results obtained in various analyses.

In the introduction the present concepts of urinary physiology are briefly but thoroughly considered to give a basis for later evaluations of laboratory findings.

A chapter is devoted to the collection and preservation of urine for various analyses. As so many specimens are collected and preserved improperly, this section is of great value to the office assistant.

The somewhat involved mathematical calculations necessary in determining renal functional tests are simplified as much as feasible. Exact instructions as to methods for performing the tests from the injection of test substances to the calculations of the results are set forth. This chapter is what many physicians have long sought for.

A brief section is devoted to the endocrine aspects of the urine and the methods of pregnancy diagnosis are enumerated. A discussion of the accuracy of the tests and applications in conditions other than pregnancy is included and is quite satisfactory for the practitioner. No bacteriologic methods of urine examination are given but presumptive methods such as smears are presented. This is frequently sufficient in the office laboratory. There are a number of errors in proof reading that are easily picked up.

H. F.

NEUERE ERGEBNISSE AUF DEM GEBIETE DER KREBSKRANKHEITEN. Fortbildungskurs der Berliner Akademie für ärztliche Fortbildung (vom 19. bis 26. Oktober, 1936). Herausgegeben von PROF. DR. C. ADAM und PROF. DR. AULER. Forty-four Contributors. Mit einem Vorwort von GEHEIMRAT PROF. DR. BORST, München. Pp. 366; illustrated. Leipzig: S. Hirzel, 1937. Price, Paper, Rm. 12; Bound, Rm. 13.50.

THIS book is based upon a series of lectures delivered by 47 specialists in oncology. The aim of these lectures was to present to practicing physicians a survey upon the more important phases of cancer research, and particularly, to discuss the newer advances made.

A great variety of subjects are covered. There are lectures on the significance of the experimental study of cancer, the etiologic relation of virus to cancer, the factors of heredity and race, and many other problems of like interest. Two chapters deal with the occurrence of tumors among domestic animals, and in plants. About half of the book is devoted to subjects of more specialized interest, such as carcinoma of the stomach, the lungs, the skin, the intestines, and of various other organs. Finally there are chapters on treatment with surgery, Roentgen rays and by other agents. To many of the lectures an excellent bibliography is appended.

The book is good as a survey, but it is in no sense a systematic textbook. With the present day interest in cancer, a collection of lectures such as this is welcome and fulfills a useful purpose.

B. L.

APPLIED PHARMACOLOGY. By A. J. CLARK, M.C., M.D., F.R.C.P., F.R.S., Professor of Materia Medica and Pharmacology in the University of Edinburgh, etc. Pp. 678; 84 illustrations. Sixth edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1938. Price, \$5.00.

For this edition the book has been rearranged and a considerable amount of new material dealing with hormones, vitamins, and chemical transmitters has been added. Considering its relatively small size, the amount of information is surprising, and this is particularly true of the résumés of the

physiology of the various body systems which precede discussions of the actions of drugs upon them. In some respects, notably the biochemistry of drug actions, this book is so modern as to be ahead of its time, affording a glimpse of what the pharmacology of the future may look like; in other respects it is behind the times. This is to be expected, since one of its chief merits is brevity achieved by selection of material which the author deems most valuable. For a complete presentation of all the available facts other books must be consulted. The book deserves high recommendation for the physician and student as a stimulating, modern presentation of the existing physiologic and biochemical basis for therapeutics.

C. S.

ERBKRAKHEIT UND FERTILITÄT. Mikropathologie der Spermien erkrankter Männer. von DR. MED. ET MED. VET. H. STIASNY, Assistent der chirurgischen Abteilung des städtischen Krankenhauses "Am Urban," Berlin, und DR. MED. K. D. J. GENERALES, JR., Lowell, Mass. z. Zt. Volontärassistent der chirurgischen Abteilung des städtischen Krankenhauses "Am Urban," Berlin, Mit einem Geleitwort von PROF. DR. ERWIN GOHRBANDT. Pp. 163; 60 illustrations, 21 tables (16 in colors). Stuttgart: Ferdinand Enke, 1937. Price, Paper, Rm. 27.; Bound, Rm. 29.

THE authors have availed themselves of the extraordinary clinical opportunity resulting from the German law of July 14, 1933, to study the correlation between fertility and heritable disease. Their attention has been directed principally to the morphology of the spermatozoa. In healthy fertile men it was found that 19% of the spermatozoa could be classified as morphologically abnormal; in men suffering from inheritable disease it averaged that 63.85% of the spermatozoa were abnormal. Actual figures ranged from 75.1% abnormality in chronic alcoholism to 53.8% in schizophrenia. It was impossible, however, to correlate the type or degree of abnormality to any specific heritable disease. This very excellent monograph is profusely illustrated with microphotographs and colored drawings of the various types of abnormal spermatozoa.

B. H.

FEARFULLY AND WONDERFULLY MADE. The Human Organism in the Light of Modern Science. By RENÉE VON EULENBURG-WIERNER. Pp. 472; 17 illustrations. New York: The Macmillan Company, 1938. Price, \$3.50.

THIS book attempts in a brief compass to express for the layman or the elementary student the basic facts of life. This difficult task has been admirably achieved. The facts are simply stated without undue use of technical terms; where technical terms are employed they are adequately explained. The ground is covered in an amazingly small number of pages, but in spite of this there is so much detail that the average physiologist will learn much that he has not previously known. The information given is amazingly accurate, considering the scope of the book. The layman should find it of great interest, even that part which may prove not completely intelligible owing to its complexity. Students of biology entering this field will find the statements clear and concise, but giving many facts for digestion and later assimilation.

However, the outstanding contribution of the book is the author's point of view. Looking at biology from the detached viewpoint of the philosopher, she regards physiologic statements as being made in terms of matter which probably does not exist in the concrete form which we commonly

attribute to it. She quotes Eddington's statement that if one could condense the protons and electrons that constitute the average adult body to a perfect solid, the mass would be just barely visible by the use of a microscope. She regards therefore the materialistic conceptions of the physiologist as mere conventions used to express partial knowledge of very complex situations. She says "Man cannot penetrate beyond the image of his mind, beyond the manifestation of energy which he himself is." The layman or the student commencing the study of biology cannot remember too often that the statements that he learns are only partially true. Any biologist or other scientist would be wise also to remind himself frequently of this fact. The book should be of much value to many different types of readers.

H. B.

GENITAL ABNORMALITIES, HERMAPHRODITISM, AND RELATED ADRENAL DISEASES. By HUGH HAMPTON YOUNG, M.A., M.D., Sc.D., F.R.C.S.I., D.S.M., Professor of Urology, The Johns Hopkins University; Visiting Urologist, Brady Urological Institute, The Johns Hopkins Hospital. Pp. 649; 379 illustrations, containing 534 drawings by WILLIAM P. DIDUSCH. Baltimore: The Williams & Wilkins Company, 1937. Price, \$10.00.

APHRODITE, as a result of a celestial union with Hermes, brought forth an extraordinary child, one endowed with the attributes of both father and mother. Unable to determine the sex, they decided to affix both their names, and their child has gone down in history as Hermaphroditos. After this picturesque and mythical origin, these unfortunates have suffered cruelly from the advancing standards of morals and have found scant comfort from the attentions of lawmakers, historians, mythologists, poets, sculptors, painters and physicians.

The author of this unique monograph intended originally to present a group of remarkable genital abnormalities which he had encountered and treated surgically; but both interest in the subject and scope of opportunity grew, unfolding unexpected and hitherto undescribed conditions—anatomic, pathologic, endocrine and psychologic—which were intimately associated with each clinical problem. This large and well-illustrated volume presents his trials and successes with 55 cases of the most extraordinary examples of embryologic dysfunction and congenital abnormality that have ever been assembled. Divided into 22 chapters, the material ranges from the simple cases of hypospadias and epispadias (with depiction of the author's original and successful operative corrections) through his 17 cases of pseudohermaphroditism to culminate in the addition of the twentieth proven case, in the world's literature, of hermaphroditismus verus. Likewise are incorporated his 6 cases of adrenalectomy and a complete discussion of the adrenal-genital syndrome. Perhaps the most outstanding feature is the excellent result of the combination of the author's exquisite surgical technique and the artist's ability to depict the operative steps by his brilliant illustrations. It is a unique and an intensely human document, which lends a promise of a happier future to these unfortunate social pariahs.

A. R.

THE NEGRO'S STRUGGLE FOR SURVIVAL. A Study of Human Ecology. By S. J. HOLMES, Professor of Zoölogy in the University of California. Pp. 296; 10 illustrations and 50 tables, also appendix of 31 tables. Berkeley, Calif: University of California Press, 1937. Price, \$3.00.

THIS monograph deals with a subject which has stimulated much speculation, but little of scientific value, dealing directly with the whole subject, has been contributed. "The biological trend of the American negro cannot

fail to have an important influence upon the people of the United States in many ways," as the author states.

He has made a thorough study of the problem of the survival of the negro from the biologist's point of view and collected much material bearing on the interracial struggle for existence between the white and colored races in this country. The factors influencing the growth and the limitations of the negro race, the effects of negro migration, of interbreeding with the white race and other biologic phenomena observable in the negro race are discussed. The interpretation of all the interacting factors and the ultimate outcome of the complex biologic problems which the coexistence of the two races creates cannot be foretold. The author has, as he says, been brought face to face with a number of uncertainties which allows only a discussion of possibilities which may influence future national policies. No one can say what the ultimate fate of the negro in America is to be. This book is a scholarly analysis of the problem, and contains much material derived from the field of medicine regarding the relative effects of disease on the white and colored races.

G. R.

THE BIOLOGY OF PNEUMOCOCCUS. The Bacteriological, Biochemical, and Immunological Characters and Activities of *Diplococcus Pneumoniae*. By BENJAMIN WHITE, PH.D., with the collaboration of ELLIOTT STIRLING ROBINSON, M.D., PH.D., and LAVERNE ALMON BARNES, PH.D. Pp. 799; illustrated. New York: The Commonwealth Fund, 1938. Price, \$4.50.

A MONOGRAPH on the pneumococcus is opportune at a time like the present, when the attention of the public is being attracted to the pneumococcus and pneumococcal pneumonia. This book fills a considerable want. The completeness with which the author has treated such phases of the pneumococcus as its history, biochemistry, dissociation, pathogenicity, chemical constitution, specific polysaccharide-splitting enzymes, antigenicity, immunology, chemotherapy, production of antipneumococci serum and the serum treatment of lobar pneumonia makes the book valuable to the student, teacher, laboratory worker and clinician; in fact, valuable to almost anybody with a more-than-average interest in science or medicine. The research worker, no matter what phase of the pneumococcus he may be investigating, has here a valuable aid. The appendix, containing methods for preparation of the more important media, isolation and type determination of the pneumococcus, preparation of bacterial enzymes capable of decomposing capsular polysaccharides, serologic reactions and directions for the production and testing of diagnostic and therapeutic antipneumococcal serum, makes the book a valuable reference work in any laboratory. The bibliography of 1593 articles gives some idea of the thoroughness of the book and its potential value to any user.

H. M.

DIGESTIVE TRACT PAIN. Diagnosis and Treatment, Experimental Observations. By CHESTER M. JONES, M.D., Assistant Professor of Medicine, Harvard University; Physician, Massachusetts General Hospital. Pp. 152; 5 illustrations. New York: The Macmillan Company, 1938. Price, \$2.50.

THIS brief monograph deals with the type and location of pain which follows distention of various portions of the gastro-intestinal tract. It is based on a series of careful experiments in which a balloon attached to the distal end of a rubber tube was introduced, under the fluoroscope, to any desired region from esophagus to rectum and then distended until

pain was produced. The character and location of the pain was carefully observed. The results are epitomized in a series of clear diagrams. The latter chapters consist of brief abstracts of clinical cases in which especial attention is directed toward localization of gastro-intestinal lesions, using as a guide the data obtained from the experimental study. Their intensely practical value becomes apparent when one observes that careful analysis of the nature and location of digestive tract pain is in itself often as diagnostically informing as more elaborate and costly study. The author is to be commended both on the content of the monograph and on its brief, direct presentation. K. E.

FRACTURES AND DISLOCATIONS FOR PRACTITIONERS. By EDWIN O. GECKELER, M.D., Fellow of the American College of Surgeons; Fellow of the American Academy of Orthopædic Surgeons. Pp. 252; 213 illustrations. Baltimore: William Wood & Co., 1937. Price, \$4.00.

THE author states that the purpose of the book is to condense the subject of fractures and dislocations without the omission of important details. This little volume has 32 chapters and a short bibliography at the end of each chapter. Some of the sections are so short that they might well have been excluded. The material dealing with bone repair is totally inadequate for even a fair knowledge of the process. Without any preliminary explanation, the statement is made that "It is well known that phosphatase is found in large quantities at the site of fractures." There are numerous similar instances in the text. Although the volume is intended in large part for use by general practitioners such subjects as subcutaneous leverage, transfixion and even open reduction are discussed. The dangers of attempting to do this in so small a volume are self-evident. There is, however, much in this little volume which will be of interest to general practitioners. The sections on roentgenograms and the medico-legal aspects of fractures are good.

The work will be of value to students who wish rapidly to review the subject and to practitioners who want a small ready reference volume. Many of the fractures discussed such as fractures of the vertebræ, pelvis, humerus, femur, etc., are best treated by men who have had special training in fracture work and who have affiliations which permit of hospitalization. From this viewpoint, if the book was even in part intended for surgeons interested in fractures the volume is much like a compendium. The illustrations are good, and the type and paper excellent. The index is complete. I. R.

THE RÔLE OF CHEMIOTAXIS IN BONE GROWTH. By A. P. BERTWISTLE, M.B., CH.B., F.R.C.S. (EDIN.). Pp. 59; 32 illustrations. London: Henry Kimpton, 1937. Price, 8/6.

THIS monograph, by a British roentgenologist, deals with normal and pathologic bone growth. A law is propounded "that whenever young fibrous tissues, particularly young blood-vessels, come into contact with bone or a calcified deposit, new bone formation occurs." The fibrous tissue growth contacts the bone or calcium deposits as a result of "disruptive chemotaxis." The term "disruptive chemotaxis" is defined as "the power of certain hard substances of attracting and drawing into themselves certain soft, living substances." The thesis is interesting, not entirely new, and certainly not proven by the author, who is handicapped by thinking in terms of the gross pathology of the roentgenologist rather than in the terms of the cellular changes of the pathologist. G. W.

PRIMARY CARCINOMA OF THE LUNG. By EDWIN J. SIMONS, M.D., Member of the Staff, St. Gabriel's Hospital, Little Falls, Minn., and Lymanhurst Health Center, Minneapolis, Minn.; Visiting Consultant in Medicine, Minnesota State Sanatorium, Ah-gwah-ching, Minn. Pp. 263; 30 illustrations and 1 colored plate. Chicago: The Year Book Publishers, Inc., 1937. Price, \$5.00.

THIS small monograph on primary carcinoma of the lung was written by a general practitioner for general practitioners. It will, however, prove of interest to internists, surgeons, roentgenologists and pathologists. The historical aspects and incidence in this and other countries, the etiology and pathology of the condition are carefully covered, though it is pre-eminently clinical in its approach. Diagnostic methods which can be used by the general practitioner or specialist, and differential diagnosis are fully reviewed. Sputum and pleural fluid examination is described and the use of bronchoscopy as a diagnostic aid is included. The various methods of therapy are comprehensively covered; symptomatic treatment, radiation, bronchoscopic treatment and surgery. More than 5000 proven cases of pulmonary cancer are analyzed. The bibliography includes approximately 500 papers. In the preparation of the work the author had had the advice of Wangenstein, Rienhoff and Graham, and has drawn freely from the works of leaders in the field of pulmonary diseases.

The illustrations are excellent. It is, I believe, the best available short monograph on the subject. It can well be compared with Alexander's monograph on the *Surgery of Pulmonary Tuberculosis*, written some years ago. Here is a volume that should find a place in the library of many physicians and specialists. They will all be wiser for having read it.

I. R.

SYNOPSIS OF DIGESTIVE DISEASES. By JOHN L. KANTOR, PH.D., M.D., Associate in Medicine, Columbia University; Gastroenterologist and Associate Roentgenologist, Montefiore Hospital for Chronic Diseases, New York. Pp. 302; 40 illustrations. St. Louis: The C. V. Mosby Company, 1937. Price, \$3.50.

THIS small volume is divided into 4 sections, dealing with: 1, Such general considerations as diagnostic and therapeutic methods, functional and allergic disturbances of the gastro-intestinal tract; 2, a systematic description of digestive disease from mouth to anus; 3, diseases due to intestinal parasites; and 4, digestive symptoms of extradigestive disease. It is obvious that the synoptic treatment of such a vast field requires a brevity which is at one time a boon to the student and busy practitioner, and a strict limitation of the usefulness of the volume. The author's wide experience makes him well qualified to condense the material into a practical compend. Its only shortcomings are inherent in the very nature of an epitome rather than in the selection and presentation of its contents.

K. E.

EXTERNAL DISEASES OF THE EYE. By DONALD T. ATKINSON, M.D., F.A.C.S., Consulting Ophthalmologist of the Santa Rosa Infirmary and the Nix Hospital, San Antonio, Texas; Fellow of the American Academy of Ophthalmology and Oto-Laryngology. Pp. 718; 494 illustrations. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1937. Price, \$8.00.

THIS book deals with those conditions of the eye which do not require elaborate equipment for diagnosis. There are no recent publications in English covering only this field. However, the author has included in this

edition brief reference to slit lamp microscopy and to orthoptic training. The numerous illustrations, many from drawings or wax models by the author, are almost diagrammatic in the method of presenting the pathologic lesion illustrated. In the last section of the volume is a convenient ophthalmologic formulary.

The text deals with glaucoma, cataract and conditions of the ocular muscles, as well as of conditions limited in a strict sense to the external diseases of the eye. Operative treatment and technique occupy a prominent part of each section of the book. The experiences and the preferences of the author are presented.

The volume is one that should be particularly useful to general practitioners and students. It would also be useful to one practising where ocular complications of leprosy are seen.

W. F.

LOVE AND HAPPINESS. *Intimate Problems of the Modern Woman.* By I. M. HOTEP, M.D. With a Prefatory Note by LOGAN CLENDENNING, M.D. Pp. 242. New York: Alfred A. Knopf, 1937. Price, \$2.00.

THIS book deals with the little discussed side of the conflict between the basic instinctive drive for sexual satisfaction and the restricting forces of moral, religious and social ideals. It gives sanction and solace to the satisfying of these instincts, stating frankly the dangers encountered, the price paid, and the difficulties encountered in this procedure, and briefly (and glibly?) gives suggestions for coping with these factors.

The tone and temper of the book is a bit disappointing for one with the background of the author, "I. M. Hotep (?)," and the reader wonders if the frustrated female coming for help will be able easily to lay aside moral, religious and social scruples as is suggested. The crying need for revision of divorce, contraception and abortion laws to meet modern needs more adequately is forcefully stressed. This portrayal of a controversial subject, under correct supervision and guidance, can be of distinct use in handling this type of problem.

L. S.

A PRACTICE OF ORTHOPEDIC SURGERY. By T. P. McMURRAY, M.B., M.Ch., F.R.C.S. (Edin.), Director of Orthopedic Studies and Lecturer in Orthopedic Surgery, Liverpool University; Honorary Orthopedic Surgeon, David Lewis Northern Hospital, etc. Pp. 471; 178 illustrations. Baltimore: William Wood & Co., 1937. Price, \$5.00.

THIS excellent volume is dedicated to Sir Robert Jones. The author has in compact and concise form given a description of the basic principles underlying the treatment of orthopedic surgery. The details of many operative procedures have been wisely omitted. No reference is made to the treatment of fractures. There are 25 chapters and a very satisfactory index. The entire text is written from the point of view that "As orthopaedic surgery is concerned largely with growing and developing tissues the outlook of the surgeon should be essentially conservative." Some American orthopedists will not agree fully with this conception but to the Reviewer the case which the author makes for it is a good one. The viewpoint that medicine and surgery are interdependent is constantly kept in mind and adds greatly to the value of the work. The photographs are clear, the roentgen ray reproductions good and the diagrammatic sketches excellent.

Covering splints and apparatus, adhesions and ankylosis, the various joints and their diseases, the spine, the feet, the sequelæ of poliomyelitis, certain injuries to peripheral nerves, the affections of muscles and tendons,

rickets, and the general dyscrasias and tumors of bone in a single small volume is an accomplishment. To have done this so that it proves valuable to general practitioner, general surgeon and specialist is a real achievement.

I. R.

CONTRIBUTIONS TO MEDICAL RESEARCH. Anniversary Volume. Scientific Contributions in Honor of Joseph Hersey Pratt on His Sixty-fifth Birthday. (Reprinted from articles appearing in *Annals of Internal Medicine*.) By HIS FRIENDS. Pp. 983; illustrated. Printed by Lancaster Press, Inc., Lancaster, Pa., 1937. Price, \$7.00.

THE sixty-fifth birthday of Joseph Hersey Pratt, M.D., of Boston, was recently celebrated and the event felicitously memorialized by his friends in the profession coöperating to publish this volume in his honor. It would be impossible properly to review in the, necessarily, limited space of this column the 80 interesting medical presentations by Dr. Pratt's friends and associates. In the Reviewer's opinion each essay may be read with sustained interest and pleasure.

One also finds listed the references to 120 contributions to medical literature by Dr. Pratt. The first article appeared, in 1895, while Dr. Pratt was an undergraduate medical student, and the latest was published in 1937. For a doctor to have acquired 65 birthdays is, in the natural order of things, commonplace; but to have utilized those years as wisely, kindly and altruistically as Joseph Pratt has done is exceptional and noteworthy. One frequently hears, within and outside the medical profession, the trite but, unfortunately, true statement, "there are too many doctors." Alas! one will never live to hear the statement, "there are too many kind, skilled and excellent physicians." Joseph Hersey Pratt, M.D., represents the medical profession at its best. He is learned, talented and skilled and is second to no other physician of his own, or any other city, in kindness and consideration for others. He is an inspiring teacher and, like all truly great physicians, he continues to be a life long student of medicine. May he long be spared to his patients, his profession, his friends, and to the citizens of that delightful city, Boston.

J. B.

A TEXTBOOK OF HEMATOLOGY. By WILLIAM MAGNER, M.D., D.P.H., Pathologist, St. Michael's Hospital, Toronto, Canada; Lecturer in Pathology, University of Toronto, etc. Pp. 395; 23 illustrations, 3 colored plates and 3 charts. Philadelphia: P. Blakiston's Son & Co., Inc., 1938. Price, \$4.50.

In the preface the author states his purpose: to present the subject of hematology "in a manner acceptable to practising physicians as well as to those primarily interested in the study of disease by laboratory methods." These twin purposes (which are to a disturbing degree definitely dissimilar twins) are approached with creditable modesty, accuracy and simplicity. The binding of the handy-sized volume is said to be "sturdy, cleanable, water resisting and vermin proof." The format is pleasing, the print large and clear, the index comprehensive and the bibliography well selected. The photomicrographs, as is generally true, are not of much value to the uninitiated; and the case reports incorporated in the text should perhaps have been presented in small type, if at all. Your Reviewer recommends this book to junior and senior medical students, internes, and energetic practitioners who want a "conservative" review of current (1937) hematologic methods, views and findings.

T. F-H., Jr.

PULMONARY TUBERCULOSIS IN PRACTICE. A Modern Conception. By R. C. WINGFIELD, B.A., M.B., B.Ch., F.R.C.P., Medical Superintendent, Brompton Hospital Sanatorium, Fimley; formerly Tuberculosis Officer, St. Thomas's Hospital. Pp. 122; 25 illustrations, and 1 insert (in color). Baltimore: William Wood & Co., 1937. Price, \$2.50.

A NEED is filled by this compact volume, which is designed to enable the family physician to detect tuberculosis at a readily curable stage, and to coöperate with the tuberculosis specialist in the management of the tuberculous patient when sanatorium care is refused or completed. The introductory chapters, which summarize modern concepts of pathogenesis, emphasize that only in the end stages of disease are the classical symptoms and signs of pulmonary tuberculosis obtained. The insidious clinical manifestations of minimal tuberculosis are described in detail, with stress on the need and indications for roentgenologic examination. The broad principles of treatment are discussed, with elaborate consideration only of details of direct concern to the practitioner. H. I.

INTRODUCTION TO OPHTHALMOLOGY. By PETER C. KRONFELD, M.D., Professor of Ophthalmology, The Peiping Union Medical College. Pp. 331; 32 text illustrations and 5 plates. Springfield, Ill.: Charles C Thomas, 1938. Price, \$3.50.

THIS very interesting book is intended to supplement a textbook of ophthalmology for the undergraduate medical student. It is not intended as a textbook and could not be used as such. It contains much of interest to practising ophthalmologists and can be recommended for its original points of view. F. A.

THE BRAIN AND ITS ENVIRONMENT. By JOSEPH BARCROFT, Professor of Physiology, Cambridge University. Pp. 117; 30 illustrations. New Haven: Yale University Press, 1938. Price, \$2.00.

THIS series of 3 lectures was delivered under the auspices of a foundation devoted to "application to human welfare . . . by the building up of the truths of science and philosophy into the structure of a broadened and purified religion." Without this clue we should be puzzled to account for the title under which masquerades an interesting account of the author's recent work upon the physiology of the sheep embryo.

The first lecture presents an analysis of fetal movement; the second deals with the shifts at birth in blood-vessels, blood gases and their transport, and respiration. Up to this point, an array of new results is woven into a logical pattern with the clarity and charm of the author at his best. The last chapter sketches the familiar picture of the nervous responses to extreme shifts in tension of the blood gases in the adult human.

G. McC.

NEW BOOKS.

A Textbook of Clinical Pathology. Edited by ROY R. KRACKE, Emory University, Georgia, with the assistance of DOCTORS A. P. BRIGGS, L. W. DIGGS, GEORGE HERRMANN, F. M. JOHNS, F. B. JOHNSON, R. MCBURNEY, H. E. MELNEY, A. J. MILLER, F. P. PARKER, V. P. SYDENSTRICKER and J. G. WAHLIN. Pp. 567; 205 illustrations and 31 plates (19 in color). Baltimore: William Wood & Co., 1938. Price, \$6.00.

The Anemias. With Special Reference to Pernicious Anemia and the Use of Liver Extracts and Supplementary Factors in the Treatment of Anemias. Supplement. Blood Morphology in Diagnosis. A Series of Six Articles Reprinted from The Physician's Bulletin. Pp. 98; 7 colored plates. Indianapolis: Eli Lilly and Company, 1938.

Leukemia and Allied Disorders. By CLAUDE E. FORKNER, A.M., M.D., Assistant Professor of Clinical Medicine, Cornell University Medical School, and Assistant Attending Physician, New York Hospital, etc. Pp. 333; 73 illustrations and 6 colored plates. New York: The Macmillan Company, 1938. Price, \$5.00.

Athletic Injuries. Prevention, Diagnosis and Treatment. By AUGUSTUS THORNDIKE, JR., M.D., Surgeon in the Department of Hygiene, Harvard University; Assistant in Surgery, Harvard Medical School, etc. Pp. 208; 104 illustrations. Philadelphia: Lea & Febiger, 1938. Price, \$3.00.

League of Nations. Bulletins of the Health Organisation. Vol. VI, No. 5 (October, 1937) and No. 6 (December, 1937). Pp. 211 (No. 5), 258 (No. 6). New York: Columbia University Press, 1938. Price, 65c each.

Pediatric Surgery. By EDWARD C. BRENNER, A.B., M.D., F.A.C.S., Director of Surgery, Riker's Island and Detention Hospitals; Attending Surgeon, Midtown Hospital, etc. Pp. 843; 293 illustrations. Philadelphia: Lea & Febiger, 1938. Price, \$10.00.

The Biological Standardisation of the Vitamin. By KATHARINE H. COWARD, D.Sc., Reader in Biochemistry, University of London; Head of the Nutrition Department, Pharmaceutical Society of Great Britain. Pp. 227; 44 figures and 29 tables. Baltimore: William Wood & Co., 1938. Price, \$4.50.

Thoracic Surgery. A revised and abridged edition of Sauerbruch's *Die Chirurgie der Brustorgane*. By FERDINAND SAUERBRUCH, Professor of Surgery in the University of Berlin, and LAURENCE O'SHAUGHNESSY, F.R.C.S., Hunterian Professor in the Royal College of Surgeons of England; Consulting and Thoracic Surgeon to the British Legion Sanatorium, Preston Hall, and to the Nottinghamshire County Council, etc. Pp. 394; 215 illustrations and 15 colored plates. Baltimore: William Wood & Co., 1937. Price, \$13.50.

Christianity and Sex. By RICHARD C. CABOT, M.D. Pp. 78. New York: The Macmillan Company, 1938. Price, \$1.00.

Essentials of Obstetrical and Gynecological Pathology with Clinical Correlation. By MARION DOUGLASS, M.D., F.A.C.S., Assistant Professor of Gynecology, Western Reserve University; and ROBERT L. FAULKNER, M.D., Senior Clinical Instructor in Gynecology, Western Reserve University. Pp. 187; 148 illustrations. St. Louis: The C. V. Mosby Company, 1938. Price, \$4.75.

Internships and Residencies in New York City, 1934-1937. Their Place in Medical Education. Report by The New York Committee on the Study of Hospital Internships and Residencies. JEAN ALONZO CURRAN, M.D., Executive Secretary. Pp. 492. New York: The Commonwealth Fund, 1938. Price, \$2.50.

This study, sponsored in 1934 by the Commonwealth Fund, has been carried on by a large committee of New York physicians. The report deals with such topics as "Resources for Intern and Graduate Education in New York City;" "The History of Internships and Residencies;" "The Relation of Intern and Graduate Education to Practice: A Survey of 1904 Practicing Physicians, Graduates of New York City Medical Colleges;" "Geographic Distribution of the Medical Colleges Supplying House Staffs to New York City Hospitals;" "Factors Contributing to House Staff Efficiency;" "Hospital Libraries and Their Use;" "Preparation and Training of the Intern;" "Organization of the Internship Program and Capacity of the Hospital in Relation to Quality of the Internship;" "Residencies and Fellowships in New York City Hospitals." There are 160 pages of appendices, including an 18-page bibliography.

Les Épidémies et Les Perturbations Électromagnétiques du Milieu Extérieur. By PROF. DR. A.-L. TCHJEVSKY. Pp. 239; 120 illustrations. Paris: Editions Hippocrate, 1938. Price, 40 fr.

Some Account of the Pennsylvania Hospital From Its First Rise to the Beginning of the Year 1938. By FRANCIS R. PACKARD, M.D. Pp. 133; illustrated. Philadelphia: Printed by the Engle Press for the Pennsylvania Hospital, 1938. Price, \$2.50. (Books are obtainable from the Pennsylvania Hospital, 8th and Spruce Streets, Philadelphia, Pa.)

Advances in the Therapeutics of Antimony. By PROF. DR. PHIL. NAT. HANS SCHMIDT and DR.-MED. F. M. PETER. With a Preface by DR. PHILIP MANSON-BAHR, C.M.G., D.S.O., M.D., F.R.C.P. Pp. 257; 10 illustrations. Leipzig: Georg Thieme, 1938. Price, Paper, M. 18; Bound, M. 19.50.

Papworth. The Sims-Woodhead Memorial Laboratory. Research Bulletin for 1937. Vol. 1, No. 2. Illustrated. Papworth: Pendragon Press, 1938.

Human Powers and Their Relations. By K. W. MONSARRAT. Pp. 289; 60 figures. London: Hodder & Stoughton, Ltd., 1938. Price, 10/6.

NEW EDITIONS.

Klinik und Therapie der Herzkrankheiten und der Gefässerkrankungen, Vorträge für Praktische Aerzte. By PRIVATDOZENT DR. D. SCHERF, in Wien. Pp. 319; 10 illustrations. Fourth edition. Wien: Julius Springer, 1938. Price, Paper, Rm. 7.20; Bound, Rm. 8.40.

A Diabetic Primer for Children. By ALFRED E. FISCHER, M.D., Adjunct Pediatrician and Chief of the Children's Diabetic Clinic, Mount Sinai Hospital, New York City, etc. Pp. 53 (lithoprinted). Second edition. Privately published. Copies may be obtained from Dr. Alfred E. Fischer, 73 East 90th St., New York City.

Pharmaceutical Latin. For Pharmaceutical, Medical, Dental and Veterinary Students and Practitioners. By JACOB S. DORFMAN, Assistant Professor of Pharmacy, Columbus University College of Pharmacy, etc. Pp. 146. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, \$2.00.

Tuberculosis Among Children and Young Adults. By J. ARTHUR MYERS, PH.D., M.D., F.A.C.P., Chief of Medical Staff and Director of Tuberculosis Activities, Lymanhurst Health Center; Professor of Preventive Medicine, University of Minnesota. With Chapters by C. A. STEWART, M.D., PH.D., Clinical Professor of Pediatrics, University of Minnesota; PAUL W. GIESLER, M.D., F.A.C.S., Assistant Professor of Orthopedic Surgery, University of Minnesota. An Introduction by ALLEN K. KRAUSE, M.D., Lecturer in Medicine, Johns Hopkins University. Pp. 401; 71 illustrations. Second edition. Springfield, Ill.: Charles C Thomas, 1938. Price, \$4.50.

Progressive Relaxation. A Physiological and Clinical Investigation of Muscular States and Their Significance in Psychology and Medical Practice. By EDMUND JACOBSON, A.M., PH.D., M.D., Laboratory for Clinical Physiology, Chicago. Pp. 494; 89 illustrations and 10 tables. Revised edition. Chicago: The University of Chicago Press, 1938. Price, \$5.00.

Die Chirurgie des Kropfes. By HOFRAT DR. KARL URBAN, Vorstand der chirurgischen Abteilung und Leiter des Krankenhauses der Barmherzigen Schwestern in Linz a. D. Pp. 112; 51 illustrations. Second edition, enlarged. Wien: Franz Deuticke, 1938. Price, Paper, M. 7; Bound, M. 9.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
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PELLAGRA.

IN the 200 years since pellagra was first recorded in medical literature, few diseases have equalled it in the elusiveness of its etiology, the scope of its clinical aspects and the disappointments in its treatment. Casel recorded the disease in the Asturias in 1735. Pujati, of Venice, described it about 1755, but its recognition by Italian physicians was known as far back as 1720.⁷¹ Frapolli named the disease pellagra in 1771. Estimates show that by 1830, about 5% of the population of northern Italy had pellagra. The diagnosis of the disease in France, the Balkans, Egypt and, in 1863, in the United States, established many widespread endemic areas and led eventually to the recognition of its world-wide distribution. Endemic centers have also been found in India, Japan, Australia, South America and Mexico. Sporadic cases have been reported in practically all lands.

Etiology. The exact cause of pellagra is unknown. The disease was early associated with the food habits of its victims, a contention which, although changed entirely in its interpretation, is the main thesis of most investigators today. Ideas of etiology have been colored naturally both by the experiences of the investigators putting them forth, and by the general concepts of disease in the corresponding era. Indeed, the evolution of medical thought in the past 200 years may be seen in the changing views on the etiology of pellagra.

Maize. Early association of pellagra with the ingestion of maize directed attention to this substance as the causative agent. In 1789, "spoiled" corn was accused, and even today an association of pellagra with the ingestion of corn is held by some, despite the fact that the disease occurs in groups never having eaten maize. Also, in many races using maize as a staple diet, pellagra is conspicuously absent.^{70d} The latter fact does not fit well with recent suggestions that the low value of protein in maize as compared to that of wheat may lead to pellagra through an inadequate supply of essential proteins.⁸⁵ Stockman and Johnson⁷⁵ found that a maize diet caused death in monkeys as a result of central nervous system changes like those of pellagra. An

acid was found in maize which, when administered by stomach or hypodermically, produced the same results. Other cereals, such as rice, rye, wheat and oats, produced similar results even when the diet was rich in vitamin-containing foods. In rabbits, skin lesions and thinning of bones occurred. Still, Spies and DeWolf⁶⁶ showed that 10 pellagrins taking large quantities of corn whiskey with an adequate diet and yeast showed no toxic symptoms, indicating again a probable deficiency.

Infection. The bacterial era naturally led to the search for an infectious agent as the cause, and later the recognition of deficiency diseases to a nutritional etiology. Evidence for the infectious theory is entirely indirect and far from convincing. Such points as the seasonal character of the disease, with occurrence chiefly in the late spring and summer, symptomatic improvement with the sudden onset of cool weather and alleged cure by the use of arsenic, simulate the events in certain infectious diseases, but prove nothing. The association of the occurrence of the disease with unsanitary conditions, as pointed out by the Thompson-MacFadden Commission,⁵⁸ and the decrease in incidence of pellagra with improvements in sanitation are suggestive, but again prove nothing. The same may be said of the occasional occurrence of the disease in well-to-do families on liberal diets. Although many infectious agents, especially in relationship to infestation of the gastro-intestinal tract, have been postulated, no organism has been assignable as the cause. Inability to demonstrate an organism has led to the filtrable virus theory⁷⁸ with the skin eruption and mucous membrane lesions attributed to secondary involvement of the nervous system. Goldberger²⁶ was unable to transmit the disease from man to man. Blood intramuscularly or subcutaneously, nasal secretions by application to the mucosa of the nose and mouth, and dermal scales, urine and feces of pellagrins by mouth, administered to normal subjects, did not lead to the development of pellagra. Similar experiments in monkeys were unsuccessful.⁴⁴ Epidemiologic studies appear to be the only support of the infectious theory and Eddy and Dalldorf¹⁷ remind us that such evidence of the infectious nature of scurvy was collected and is now forgotten. One cannot accept the infectious theory until new and conclusive evidence is adduced for its support. That certain infections may play a contributory rôle to the development of pellagra will be discussed below.

Nutrition. The nutritional theory holds the center of the stage today. The lack of definite evidence for the infectious theory contrasts with the wealth of pointed and controlled investigations favoring the nutritional hypothesis. One of Goldberger's experiments has already been cited. Although he and others up to the present time have not isolated a pure chemical substance or vitamin which has been shown to be the agent missing from the diet of pellagrins, prevention and remission by the use of proper diet and the production of the disease in healthy subjects by directed limitation of their diets stand as important evidences of a deficiency as the cause. In the Army, where an adequate dietary is maintained, pellagra is very rare,²⁵ even in countries where pellagra is highly endemic. Prior to the World War, pellagra was practically unknown in the Italian, Egyptian and American armies. Although pellagra is endemic among the civilians in the area surround-

ing Fort Benning, Georgia, there has been only 1 case among the soldiers since its establishment.

The work of Goldberger and his co-workers^{26,29-31} is too well known to require detailed review here. In a period of 3 years he observed 414 pellagrins in 4 institutions. No changes were made in the conditions of living except the addition to the diet of meat, legumes and milk. Only 1 recurrence was noted under these conditions, whereas a return to the old type diet in 1 of the institutions was followed by an incidence of about 40 %, with disappearance again on resumption of the improved diet.

The production of pellagra in man by dietary control proved to be a crucial and important bit of evidence favoring the deficiency theory. Of 11 normal convicts (volunteers) placed on a pellagra-producing diet, 6 showed, in 5 months, evidence of typical dermatitis and nervous and gastro-intestinal symptoms.²⁹ Later, Walker and Wheeler³¹ repeated the same experiment, with positive results, in 17 of 18 epileptic subjects, who developed stomatitis, diarrhea and bilateral symmetrical skin lesions in approximately 6 months. A control group on the same diet plus greens showed no pellagra in 1 year.

The application of similar procedures to the dog as a test animal disclosed the development of the disease known as black tongue. The same picture has been easily reproduced by others.⁶¹ This disease is, therefore, regarded as the counterpart of human pellagra, especially since Denton¹⁶⁶ demonstrated that the lesions in the dog were very similar to those found in the intestinal tract of patients with pellagra. *Fusospirochetal* organisms present in the mouth are said to precipitate the oral lesions and act as a reliable indicator of the nutritional status.⁶¹ Blankenhorn and Spies,⁹ in showing the frequency of glossitis and stomatitis in alcoholism in the human, found in the swollen, deeply reddened, tender gums many *fusospirochetal* organisms, again suggesting a relationship to black tongue.

Dogs with experimental black tongue have been used as test animals in the evaluation of foods for their pellagra-preventive properties. Such foods as turnips, sweet potatoes, onions, carrots, milk, certain fish, lean meat, and a variety of greens, wheat germ, and especially yeast, have been shown to be valuable as pellagra-preventive agents. With the use of these and similar foods, Goldberger and Tanner²⁸ were able to demonstrate that proper diet was both preventive and curative for pellagra. As yet, no one has successfully shown that the pellagra-preventive and antiblack tongue properties of food can be separated to indicate the presence and close association of two separate factors.

Careful investigation into the economic conditions in areas in which pellagra is endemic has demonstrated satisfactorily that the endemic nature of the disease is not necessarily an indication of infectious origin.^{56b} The disease occurs chiefly in rural districts. For example, in 1932, 500 cases were reported in Virginia, and 45% of these were in 6 counties. Likewise, in the first 8 months of 1933, 48% of 717 cases in North Carolina occurred in 7 counties. A similar irregular distribution was found elsewhere. Common to these areas was the factor of a restricted food supply and the cultivation of non-food crops, such as tobacco and cotton, or devotion to rural industry, such as

mining and cotton mills. Rural sections devoted to the raising of livestock or food crops had no major pellagra problems. The seasonal incidence—40% of the cases in June in some areas—was related to the reduced consumption of fruit, fresh vegetables and milk, and regression of the disease to their increased consumption. Similarly, it has been shown that depression in the cotton market has led to an increase of pellagra in cotton-producing areas until these farmers were forced, through a lack of demand for cotton, to plant and raise a variety of food at home.

Protein Deficiency. The inability of investigators to isolate a single substance which could be regarded as the deficient agent in pellagra has led to the supposition that this disease may not be a single avitaminosis, with a pellagra-preventive vitamin, but raised the possibility of a deficiency of protein of "high biological value."⁸⁶ The latter may be either a single amino-acid deficiency, or a toxic substance, derived for example from a maize diet, which requires for its correction, or "neutralization," sufficient "good" protein.¹² Such theories as these have usually been attempts to fit modern concepts into old theories, such as the maize theory. Here, toxic corn products in the whiskey, producing alcoholic pellagra, are supposedly neutralized by "good" protein. Against the protein deficiency theory is evidence that protein in a purified form³⁵ exerts little, if any, protection in animals with black tongue, and yeast extracts, which are practically nitrogen-free,³⁴ will prevent and cure pellagra in patients on an otherwise pellagra-producing diet.

Vitamin B Complex. Since pellagra-preventive (P-P) properties remain following destruction of the heat-labile vitamin B₁, the heat-stable fraction is known to contain the essential factor, or factors. Attempts to isolate this factor by animal experimentation have led to a mass of confusing data. In 1926,²⁷ it was shown that rats on diets low in B₂, but adequate in B₁, developed dermatitis and stomatitis. These observations led the way to numerous demonstrations of a multiplicity of antidermatitis factors in the B₂ complex, with variable results depending on the species used as test animals. The isolation of the flavins suggested their possible identity as the P-P factor. György showed that vitamin B₁ and flavins did not prevent the development of dermatitis in rats, but that another substance obtained from yeast did. This he termed B₆ and thought it the same as the "Y" factor of Chiek and Copping.¹³ Bireli, György and Harris⁷ showed that at least 3 factors were present in so-called "B₂." These were lactoflavin, B₆, and the P-P factor, the last of which was apparently identical with the antiblack tongue factor. Further reports have shown that flavin is ineffective in the prevention and cure of black tongue.^{43,57} A fourth factor, the filtrate or chiek pellagra factor, was found to differ from the P-P factor by differences in distribution in foods.⁴⁰ Jukes³⁹ later showed further discrepancies in the distribution of these two factors. Pellagra has been successfully treated with preparations containing the filtrate factor,²³ but such preparations have not excluded other possible pellagra-preventive substances. Lactoflavin and B₆ have not been satisfactorily related to human pellagra,^{16a,23} and both have been shown, in their distribution, to fail to correlate with the pellagra-preventive properties of foodstuffs.⁷

The latest bidder for identification as the P-P factor is nicotinic acid. It is not identical with either flavin, vitamin B₆, or the chick dermatitis factor.^{15b} Although demonstrated by Funk in vitamin B preparations 25 years ago, present interest in this preparation has been stimulated by the demonstration of Elvehjem and his associates,¹⁹ in 1937, that nicotinic acid is active in the cure of canine black tongue, and that it is present in liver, from which they isolate it. Harris³⁶ has shown, in monkeys having the analogue of experimental human pellagra on a pellagra-producing diet containing the other known constituents of the B₂ complex, a curative effect with nicotinic acid; but warns that further work is necessary to see if nicotinic acid was the sole deficiency in such a diet. The compound is effective in the treatment of the stomatitis and dermatitis of endemic pellagra, as will be discussed later. Its place in the etiology of the pellagra is not yet settled. The evidence, given in the section on Treatment below, strongly favors the assumption that it is the P-P factor of Goldberger, a precursor of it, or one factor of a multiple deficiency state. Harris³⁶ suggests that it may be the less active form of a more active variation formed from it within the animal body.

The frequent occurrence of pellagra in the face of an adequate diet in patients with derangements of the gastro-intestinal tract, such as amebic dysentery, rectal stricture, and carcinoma of the stomach, has led to the use of the term "secondary pellagra." In such patients the gastro-intestinal disease has been assumed to interfere with the absorption or production of the P-P principle or principles. If such disease is etiologically important in the development of pellagra in these patients, the term "conditioned deficiency" may be extended to include such patients.

Multiple Deficiencies. "Why apparently identical conditions should sometimes produce pellagra, sometimes hyperchromic megalocytic anæmia, sometimes simple microcytic anæmia, sometimes polyneuritis presumably from deficiency of vitamin B₁, and most often nothing abnormal, is a complex problem that awaits solution."⁵⁹ Such inconsistencies as these and the clinical findings, together with the inadequacies of the present theories of pellagra to explain the occurrence of the disease have led Sydenstricker and his associates⁷⁶ to suggest that pellagra is a conditioned deficiency of the same order as pernicious anemia, that an intrinsic factor (from the stomach) must act with an extrinsic factor in a manner similar to the action of Castle's factors for pernicious anemia to produce an essential substance necessary for the prevention of pellagra. Others have also suggested this theory.^{49,70d} By variations in the amount of this hypothetical intrinsic factor, and the organism's ability or inability to regenerate it in the presence of adequate supplies of extrinsic factor, the response of pellagrins to therapy is explained. A prolonged deficient intake of extrinsic factor might lead to exhaustion or failure of production of intrinsic factor with the development of pellagra. In some a sufficient supply of intrinsic factor might remain or regenerate to make use of the extrinsic factor. Imitation of Castle's experiments on pernicious anemia with patients on pellagra-producing diets⁷⁶ supported the hypothesis. Some patients supposedly retain enough intrinsic factor to recover on diets deficient in B₂; others are able to regenerate the intrinsic factor rapidly

in the presence of an adequate supply of extrinsic factor and recover on high-protein feeding. Others, with the intrinsic factor totally lacking and unable to regenerate it with dietary feeding, may recover under substitution therapy, or die before such therapy is instituted. Stan-nus^{70d} has speculated on the rôle of corn, alcohol, carcinoma, and other factors in interference with production of intrinsic factor. More work and less postulation is now necessary to establish or disprove these concepts.

The idea that pellagra may be a multiple deficiency is not new.^{32,82} The numerous reports of diseases associated with stomatitis and glossitis^{70c} also suggest this possibility. Spies and Aring,⁶⁵ in studying the peripheral neuritis associated with pellagra, could not distinguish it from the peripheral neuritis of beriberi. They found that vitamin B₁ containing foods and intravenous injections of the crystalline vitamin gave prompt relief of the neuritic pain, but did not cure the glossitis and stomatitis. Nicotinic acid in 3 cases completely healed the severe stomatitis and glossitis, but did not cure the peripheral neuritis. Although all patients with pellagra do not have neuritis, these results strongly favor the multiple deficiency theory. Until a substance is isolated which will cure, by itself, the triad diagnostic of pellagra, it will not be known whether pellagra is a single disease caused by one or any deficiency, a syndrome caused by more than one deficiency, or an expression of multiple deficiencies necessarily acting together.

Photosensitization. The skin lesions, and particularly their relationship to exposure to sunlight, have led to photodynamic hypotheses. Certain diseases of animals, such as *geeldikkip*,⁵¹ a poisoning caused by the excessive feeding of Tibilus to small stock in Africa, are known to occur from the ingestion of porphyrins, which photosensitize the skin. Ingestion of hematoporphyrin by man in adequate dosage is known to produce lesions in the skin on exposure to sunlight. These effects have been reviewed recently in these columns.⁵ Observations on pellagrins by Bassi³ in Italy, in 1934, and later by Ellinger and Dojmi¹⁸ and Beekh, Ellinger and Spies⁴ have shown elevated values for porphyrins in the urine of pellagrins in the acute stages of the disease. Whether photosensitization of the skin by porphyrins is important in the production of the pellagraderm is unknown, and their source, although probably from red blood cell destruction, is obscure. Scott, Turner and Mayerson⁵⁵ were unable to detect spectroscopically the presence of hematoporphyrin in the serum of pellagrins.

Selenium is another substance which is sensitive to light and occurs in the body in minute amounts.¹ Animals eating plants containing selenium obtained from the soil may die on exposure to sunlight. The symptoms produced are gastro-intestinal, nervous and dermal.

Selenium is related to sulphur and some plants cannot distinguish metabolically between the two. Sulphur metabolism is deranged in pellagra, as Payne and Perlzweig⁴⁸ have reaffirmed. The increased urinary excretion of sulphates and the reduction of sulphur in the central nervous system in pellagra prompted these observers to study the sulphur content of the fingernails. In 14 cases with extensive dermatitis, the cystine content was markedly reduced while the total protein content remained unchanged. With improvement, and in partially or completely cured cases as well as in those without dermatitis, there were no marked changes.

Studies are under way to determine the distribution of selenium in the soils.⁴² Results of such investigations indicate that selenium is present in the soils of some districts in sufficient quantities to make it an agricultural problem. Thus far, these areas with seleniferous soils are chiefly western grazing lands and do not correspond to the areas of endemic pellagra. A relationship to pellagra, therefore, seems unlikely.

This section on etiology of pellagra may rightly end with repetition of its first statement. The exact cause of pellagra is unknown. The views on etiology are so divergent, and the approaches to the problem so different, that in the future, when the etiology is definitely known, many present concepts will seem amusing.

Pathologic Anatomy. Well-controlled observations on the pathologic changes in pellagra are few. Those of Denton^{16a} are particularly significant because of the exclusion of bodies with lesions of other unknown diseases and because autopsies were done within a few minutes after death. He found in general that the nutrition was in proportion to the duration of the disease. Gross lesions of the stomach were found in only 1 case, a pseudomembranous inflammation of the cardia. The anatomic picture at autopsy was sufficiently definite to warrant a diagnosis without clinical history. The mucous membranes of the mouth and esophagus showed a brownish-red color with and without small necrotic lesions. A dark red color of the small intestine and an intense colitis were characteristic. Such changes, together with the skin lesions, left no difficulty in postmortem diagnosis.

Skin lesions were found before erythema had appeared. The duration of these lesions, Denton believes, must, from the histologic point of view, be dated from the first subjective symptoms, such as a feeling of stiffness and tenseness before the lesions were visible. He found first a stage of injury, or fibrolytic stage, then a reactive or dermatitic stage, followed by repair, compensatory vascular ectasis or erythematous stage, and finally the cicatricial or atrophic stage. The presence of findings before the visibility of the lesion is extremely important, for, as will be stated in the sections on *Symptomatology* and *Diagnosis*, recognition of the disease before the skin eruption can be seen, pellagra *sine eruptione*, is of extreme clinical importance.

Certain of Denton's findings in the skin bear upon the etiology of the disease. There was no evidence of the skin lesions being infectious in nature. The sequence and character of the cutaneous changes were consistent with their being photodynamic effects, with a slight resemblance to some of the lesions of Roentgen ray dermatitis. However, he found that the reaction of the tongue, pharynx, and esophagus was essentially the same with stages of injury, reaction, compensatory vascular ectasis and atrophy, and that these lesions were the most constant and consistent in the disease. Yet these changes were so situated that some other factor than radiant energy must be responsible for them, and most likely for the skin lesions as well.

As far back as 1789, it was recognized that the skin lesions could not be explained by solar irradiation alone. Lesions are precipitated by irradiation, it is true, and reports are on record of the absence of lesions from the common sites when these areas are protected, as, for example, in the veiled women of Turkey. Spies^{61/} calls attention to the fact that lesions are most common in the spring and the sun's rays are most

powerful in the summer. The necessity of avitaminosis for the development of lesions would make this relationship lose importance. Still the lesions may affect any unexposed area, appear in patients confined to bed, and exposure of the entire body to sunlight may result in lesions only in the usual areas. Further discussion of the effects of sunlight in the following sections will show that a variety of trauma, such as pressure and chemical irritants, have precipitated skin lesions, and that sunlight is probably only a convenient one of many traumata capable of precipitating them.

The occurrence of Vincent's organisms in the mouth with glossitis and stomatitis has already been mentioned. Such infection occurs in pellagra as well as in black tongue. In the colon Denton found no pathognomonic changes but aggregate changes were quite characteristic. Numerous cysts formed in the crypts of Lieberkuhn, a change said to occur only in pellagra and sprue, but very infrequently in the latter.³⁷ Dilatation of the submucosal vessels and cellular infiltrations were also seen.

Lesions of the central nervous system have been interpreted both as by-products^{16a} of and as primary changes⁷⁸ in the disease. Such findings are not necessarily proportional to the acuteness and severity of the disease. The lesions themselves are non-specific, with changes in the postero-lateral and postero-median columns of the cord and in the spinal sympathetic and posterior ganglia. In the spinal cord, degeneration of the medullary sheaths in both the posterior columns and in the crossed and uncrossed pyramidal tracts may ultimately lead to gliosis. Such lesions are considered characteristic of, but do not occur exclusively in, pellagra.⁹⁰ They have been produced in dogs on deficient diets.⁸⁹

Clinical Aspects. I shall consider only the new and less well-known aspects of pellagra. The familiar three D's—dermatitis, dementia and diarrhea—make a trinity too well known to deserve comment. The fourth—death—is heralded by inadequate treatment. Stannus^{70b} says of the three D's, "while we may admire the alliterative ability of the author of this diagnostic slogan, it is probably true, if it be said, that nothing has done more to stifle the recognition of early cases and those that do not manifest what have been called the classical symptoms." In the light of the findings already mentioned, that demonstrable skin changes occur before the eruption is clinically manifest, one can well understand statements that many and possibly the majority of cases in an endemic area do not present classical symptoms and may go unrecognized. Physicians must awaken to the remarks of Stannus that pellagra is a disease presenting great variety in its picture, course and symptomatology as well as in intensity of individual symptoms. One wonders how often pellagra is masked under such diagnoses as dyspepsia, neurasthenia and colitis. Gradual deterioration of health, a tendency to hypochondriasis, mild attacks of mental depression, failure of mental and bodily vigor, periodic digestive disturbances with abdominal discomfort, constipation with attacks of diarrhea, a sore mouth or tongue, soreness at the angles of the mouth, vertigo and indefinite pains are but a few of the symptoms which may precede, at times by years, a frank attack of pellagra.^{70b}

To those physicians not seeing pellagra frequently, and especially

to those outside endemic centers, the wide variations in the course of the disease are little known. The courses of acute and chronic pellagra may be as different as those of acute and chronic leukemia, one with an acute fulminating course leading to early death, the other with exacerbations and remissions leading, with proper treatment, and here unlike leukemia, to cure.

Pellagra occurs at all ages. Statements vary particularly in respect to occurrence in children. Some⁸⁴ consider the disease rare in childhood, but others⁷² commonly find it below the ages of 12 to 15, and it has been reported under the age of 1 in breast-fed infants of pellagrous mothers. The dermatitis is said to be mild in children; and in infants, sore mouth, diarrhea, and restlessness commonly appear before the dermatitis. Some believe acrodynia to be an infantile form of pellagra.

Since 1913, Stannus has stressed as an objective sign a peculiar soreness at the angles of the mouth. This he terms "angular stomatitis," which, together with marginal glossitis, is among the earliest signs, a "prepellagrous" finding, so to speak. At this early stage similar lesions have been noted on the vulva, vagina, margin of the anus and perineum, and on the free margin of the prepuce. In the full-blown disease, lesions may appear also about the internal and external canthi and on the nostrils as well. Scrotal lesions occurred in 19 of 131 pellagrins in one series, 4 of whom had no other pellagrous exanthem. Many observers have noted this sign. The nail-bed is an often forgotten site of involvement.^{70b} Pigmentation and deformity of the nails of the fingers and toes may result. Desquamation in the interdigital clefts may occur⁶ and persist after other manifestations have disappeared.

Statements that the severity of the skin lesions does not parallel other symptoms have been proved many times. The author has often seen regressing skin lesions in the presence of ever increasing mental symptoms, terminating in death. Spies^{64a,b,d,f} has seen skin lesions regress in patients on pellagra-producing diets, while the stomatitis was increasing. He also showed that exposure of lesions to sunlight and ultraviolet radiation did not prevent healing in patients on a pellagra-producing diet.

The lack of correlation between the occurrence of skin lesions and solar irradiation in some patients has already been mentioned. Some further facts on this relationship have been uncovered by Smith and Ruffin.⁶⁰ They reviewed previous attempts to produce lesions by exposure and successfully brought out such lesions in 13 of 35 patients. After treatment with the P-P factor only 1 developed lesions on re-exposure, indicating the importance of the test in determining activity. Fouts and Zerfas²⁴ were able to elicit eruptions in the same manner. The appearance of skin lesions with no definite relationship to solar irradiation has caused much confusion in the interpretation of the genesis of the lesions. Bass^{2a} has noted lesions at points of pressure, such as over the buttocks and elbows in patients confined to bed, on the heels, groins and shoulders, over prominent veins and in areas in which skin surfaces are approximated. Irritation of the skin by heat, Roentgen radiation, or chemicals may affect the distribution of the lesions.²¹ Such evidence as this suggests that trauma plays an important rôle in

the precipitation of lesions and that sunlight is but a convenient and common one of many such traumata.

Skin eruptions other than the usual pellagra-derm are not uncommon. Most interesting is the seborrheic dermatitis to which Bass^{2b} and others have called attention. It is found most characteristically upon the nose, cheeks, forehead, and chin just below the mouth, but occurs at times elsewhere. A folliculitis^{70b} has been described in pellagra, the kerato-follicular lesions of Majocchi. Various observers^{77, 87} have noted these lesions, especially on the extensor surfaces of the arms and on the thighs, the buttocks and the torso. Clinically they fit the description of those found in avitaminosis A.⁸⁸ Sabry^{54b} has attempted to show that pemphigus is a form of pellagra, occurring in areas where pellagra, as such, is unknown. These conclusions are reached upon the hypothesis of defective oxidation of "dopa" in the skin.

Evidence of involvement of the heart in pellagrins has been brought out by Feil.²⁰ Of 38 patients with moderate to severe pellagra he found electrocardiographic abnormalities in 19 (50%), 14 of whom had no complication which might alter the electrocardiogram. He concluded that the heart is affected by pellagra. However, Porter and Higginbotham⁵⁰ found no characteristic electrocardiographic changes and explained those found by vascular or toxic complications. In 48 endemic pellagrins, they found no evidence of congestive heart failure.

Mental symptoms have been reported in as few as 4 to 15% of patients.³⁸ Again, the usual symptoms and signs will not be reviewed here. Pellagra may actually cause the mental disturbance, may act as a precipitating factor for other well-recognized types of nervous disease, or may, itself, result from mental disease which interferes with the proper intake of food. Nervous symptoms caused by pellagra may appear early in the disease, especially headache, vertigo, weakness, insomnia, burning sensations of the feet and other parts of the body, and depressive periods. Later inequality of the pupils, numbness, paralysis of the sphincters, ataxia and Romberg's sign may occur. Motor involvement may be due to peripheral neuritis. Hemiplegia and paraplegia have been described with restoration of function following adequate treatment.⁸

Certain laboratory data are of interest. Achlorhydria has been confirmed as a common finding.^{6, 47} In 107 typical endemic cases, 77 (72%) showed absence of free hydrochloric acid and the use of histamine did not change the percentage. There was no implication in this study that achlorhydria was a primary or uniformly antecedent manifestation of pellagra. In some instances following treatment normal function returned.

Both macrocytic and microcytic anemia have been found. Bone-marrow studies⁴¹ have shown megaloblastic and pro-erythroblastic characteristics but not to the same degree as in sprue or pernicious anemia. Less than half of Turner's patients^{70b} had anemia, all of the microcytic variety and varying from mild to very severe.

The association of deranged gastric function and anemia in pellagra with some resemblances to pernicious anemia, has led to many comparisons of these diseases. That pellagra is essentially different is shown by the demonstration that the gastric secretions of pellagrins contain the "intrinsic factor" of Castle. This factor should not be

confused with that postulated by Sydenstricker. It has also been shown that the chemical substance or substances in yeast effective in the treatment of pellagra is probably not the "extrinsic factor" of Castle⁶⁹ nor is nicotinic acid.⁶⁸

Turner^{79b,c} has found a tendency toward low serum albumin concentration, developing after the pellagra is manifest and remaining long after diagnostic evidence of the disease has disappeared in spite of adequate diet. He interpreted this finding as possibly the result of disturbed digestion and absorption of proteins from injury to the digestive system. Such determinations may be of value in estimating the severity of the pellagra and in furnishing one criterion of cure. Evidence of disturbed serum calcium and serum electrolyte concentration^{79d,e} and changes in the circulating blood volume^{79f} were also found.

Reference has already been made to "secondary" pellagra in relationship to defective absorption of essential dietary factors or defective production of an intrinsic factor. Regardless of the ultimate explanation of secondary pellagra, its occurrence in the presence of a wide variety of diseases of the gastro-intestinal tract, diseases usually entirely unconnected with pellagra, is quite common.^{59,79a} These lesions vary from esophageal and gastric defects, such as carcinoma, chronic gastritis, gastric ulcer with operative shunts, to ulcerative and tuberculous colitis, rectal stricture (lymphogranuloma inguinale), amebiasis, bacillary dysentery, carcinoma of the large intestine, rectovaginal fistula, and others. The frequency of pellagra in such conditions, with adequate dietary intake, emphasizes the importance of suspecting the presence of some latent defect in pellagrins with such a dietary history.

Diagnosis. The diagnosis of pellagra is purely clinical. Whether it identifies a single disease caused by a single etiologic factor or a syndrome due to more than one cause is unknown. The diagnosis may be one of the simplest or one of the most difficult in medicine. The presence of the trinity—pellagraderm, nervous and gastro-intestinal symptoms—makes diagnosis unmistakable. However, the triad is not always present. For example, Turner^{79b} found glossitis in 26 (61.9%) of 42 patients. Mental symptoms are said to occur in approximately one-third to one-fourth of the patients.

When the characteristic skin eruption is absent, certainty in diagnosis becomes most difficult. The remarks already made under Pathology and Clinical Aspects indicate this. In endemic areas where the diagnosis of pellagra *sine eruptione* may be expected with a fair degree of accuracy, approximately 60 to 70% of the patients^{70b} present the exanthem. Such groups do not, however, include patients not sufficiently ill to seek medical aid, nor those with entirely non-specific symptoms. The sore tongue, burning sensations in the feet, diarrhea, and mental symptoms may or may not, by themselves, be sufficient to suggest the diagnosis, and their recognition and possible significance depend to a great extent upon the clinical training and awareness of the diagnosis on the part of the examining physician. A perusal of the report of Stannus^{70a,c} on pellagra-like conditions will show the interested reader how frequently disease with the essential findings of pellagra, dermatitis excepted, is reported without reference to the possibility of pellagra, even in the presence of obvious food deficiency.

Diagnosis in certain diseases of known etiology when latent, sub-

clinical or with non-specific symptoms, is simplified by the isolation of the causative organism or by specific test. But in such diseases as rheumatic fever or pellagra, where no such aid exists, when typical clinical findings are absent and clinical awareness suggests the diagnosis, the seriousness of the disease is sufficient to justify error on the side of treatment for that disease. There is no doubt that a specific test for pellagra would often surprise the examiner by revealing the presence of the disease when not suspected, in much the same way as the Wassermann test brings to light a totally unsuspected syphilitic infection. Hope has arisen for such a test in the reports of rapid iodine decolorization by pellagrous blood^{11a,b} as compared to decolorization by non-pellagrous blood. Adequate confirmation of the worth of the reaction is not yet available, but it is strongly to be recommended that adequate attempts be made to evaluate this test.

Another aspect of diagnosis in pellagra concerns the recognition of related disease. I have already discussed secondary pellagra, presumably due to interference by certain diseases with the intake or absorption of the pellagra-preventive factor. Search for such conditions is particularly indicated in patients giving an adequate dietary history. Rectal stricture due to lymphogranuloma inguinale is so frequent in the colored female pellagrin entering the medical wards of Charity Hospital^{79a} that on the Tulane Services this lesion is one of the first to be sought. The diagnostic procedures necessary to determine the presence of secondary pellagra include those necessary for the recognition of the lesions already enumerated under Clinical Aspects. It is hardly necessary to add that in the presence of these conditions careful search should be made not only for the typical signs but also for the less characteristic signs of pellagra.

Treatment. Rational therapy in any disease depends largely upon etiology. Should pellagra be infectious in origin, development of specific biologic or chemical agents for its treatment would be most helpful. No such therapeutic agent has been found empirically. Intravenous sodium thiosulphate has been used⁶³ but without consistent results. Enthusiastic Egyptian reports^{54a} have not been confirmed. Similarly other drugs, such as arsphenamine, have been considered specific.⁴⁵ In the treatment of neurologic changes massive doses of iron have been used.⁶

The obvious relationship of pellagra to nutritional factors, particularly through the impetus given to such work by Goldberger and his associates, has shown that regardless of cause, nutritional therapy is highly successful. Even so, in patients with severe mental changes a downward course and death may occur in the face of such therapy.

Diet. The well-grounded routine principles of treatment will not be considered here. Prophylaxis in endemic areas depends chiefly upon methods of education of the rural poor to produce foods ensuring a varied and substantial diet. Variety is necessary, including milk, eggs, fresh meats and vegetables. Such changes in dietary habits of large groups are not easy to bring about. To compensate for these difficulties the distribution of dried powdered yeast for general consumption in endemic areas is effective, if only palliative.⁸³

Active treatment of the disease rests chiefly on an adequate diet supplemented as the stage of the disease and individual requirements

demand. In less severe cases dietary control alone is sufficient, if well balanced and high in calories (4000 or more daily).⁶⁴ Adequate rest is also essential. Foods high in pellagra-preventive properties should be ensured. These include milk, a quart a day; fresh lean meat, including liver; fresh vegetables, particularly legumes; and other foods as pointed out in the lists compiled by Sebrell.^{56a}

More severe cases, especially in the acute phases of the disease, require supplements to the diet and a rigidly outlined program to ensure success. The recently reported program of Spies, Chinn and McLester⁶⁷ has been successful not only in the alcoholic pellagra of the North, but also in the endemic variety in the South. It demands adequate professional and nursing care for the effective application of both general and specific measures. Such care is essential for the administration of supportive measures which may mean the difference between success and failure in severe cases. The caloric requirement was raised to 4500 calories, or more, per day with the intake assured by the administration of additional amounts if vomiting and diarrhea interfered. With severe stomatitis, a liquid diet was used until solid food could be taken. All patients were given 180 to 270 gm. of powdered brewers' yeast daily in 20-gm. doses in cold milk. Four patients with severe glossitis, diarrhea, and vomiting were given parenteral liver extract, 20 cc. 4 to 5 times daily, until improvement took place. Symptomatic measures were used as necessary. Under this régime 47 of 50 patients were discharged free from symptoms as compared to mortality rates of 50 % or higher elsewhere.

Since pellagra is notoriously a relapsing disease, addition of pellagra-preventing foods to the diet is necessary after hospital treatment. Measures have been enumerated above under Prophylaxis.

Yeast. The dosages of yeast and liver extract used by Spies, Chinn and McLester, as given above, are much higher than those commonly used and recommended. In milder forms of the disease smaller amounts are satisfactory. Goldberger and his associates³³ recommended 15 to 30 gm. ($\frac{1}{2}$ to 1 ounce) of yeast daily, in the form of brewers' yeast. This corresponds to 3 to 6 level teaspoonsful 3 to 6 times daily. Larger doses, approaching those used by Spies *et al.* should be given depending upon the severity of the disease. Yeast cakes and yeast tablets are not satisfactory.^{56c}

Liver. Voegtlin⁵⁰ reported on the use of liver in pellagra in 1920. Since then there have been many reports on the use of liver and liver extracts.^{56c} Much of this work, including that on black tongue, I shall pass over. In 1933, Ramsdell and Magness⁵² were successful with intramuscular extract in 2-cc. doses plus good diet. Ruffin and Smith,^{53a} in 1934, found liver extracts orally satisfactory, but found little or no improvement with intramuscular injections. These patients were kept on a pellagra-producing diet in both oral and intramuscular studies. Boggs and Padgett¹⁰ were successful with both liver diet and oral liver extract. Spies^{64c,e} administered liver extract to patients with severe stomatitis and glossitis by the intravenous and intramuscular routes. Doses as high as 80 cc. and 30 cc., respectively, were used and the diet was pellagra-producing. Within 24 hours improvement was noted and in 72 hours the lesions were healed. Ventriculin was also effective. Dosage was much higher than in the negative experiments of Ruffin

and Smith. Later the latter authors^{53b} reported that parenteral extracts were effective if given in sufficiently large doses. They pointed out that since most patients with pellagra will recover without supplemental therapy when fed a well-balanced hospital diet, liver preparations can be evaluated only by use on patients who have failed to improve on a basic diet, or who have relapsed after exposure to sunlight.

The efficacy of liver and liver extracts orally and parenterally is obvious from the above reports. Sebrell^{56c} points out that liver extracts are prepared and assayed for use in pernicious anemia. Their value in pernicious anemia does not necessarily bear any relationship to their value in pellagra so that large doses are necessary. In general, the oral administration of 75 to 100 gm. of liver extract daily rapidly cures most patients and parenteral liver is necessary only in gravely ill patients and those unable to ingest the proper diet orally. Their use supplements and does not substitute for the principles of dietary treatment already outlined.

Nicotinic Acid. The report of Elvehjem *et al.*,¹⁹ less than a year ago, that nicotinic acid is effective in the cure of black tongue has led to the widespread use in human pellagra of already available commercial preparations. Its isolation from liver suggests that the effectiveness of liver preparations is in a large part due to its presence, and that it may be the P-P factor of Goldberger. Its distribution in foods and correlation with the pellagra-preventive properties of foods is not yet known. The effectiveness of the preparation in black tongue has already been confirmed^{15b,46,74} and the cure of a similar deficiency state in pigs is on record.¹⁴

In human pellagra striking results have been reported.^{22,62,68} Patients placed on restricted diets for control periods have shown complete remission on the exhibition of nicotinic acid. The 4 patients of Fouts, Helmer, Lepkovsky and Jukes, and the 17 of Spies, Cooper and Blankenhorn showed healing of mucous membrane lesions within 48 hours. In the former series, all patients showed distinct improvement in general condition within the same period. In 1 patient, diarrhea ceased and stools were normal in 72 hours. In the latter series, glossitis, stomatitis, ptyalism, vaginitis, urethritis and proctitis did not reappear, while the patients received nicotinic acid, but the discontinuance of the drug in 1 patient while still on the pellagra-producing diet resulted in recurrence. In the first series, dermatitis began to heal in the second 24 hours and disappeared more slowly than with treatment with liver filtrate, but improvement otherwise was as satisfactory. In the latter series, erythematous lesions with intact epithelium blanched within 24 to 48 hours, but moist, ulcerated, thickened lesions did not seem to be benefited, nor was peripheral neuritis helped. Porphyrinuria was diminished. They quote Sydenstricker and Joliffe on 6 and 3 cases, respectively, with similar results. Smith, Ruffin and Smith⁶² report 1 patient in whom there were dramatic results on the skin lesions and mental symptoms. Mental confusion began to improve after 48 hours and after 6 days the patient was entirely rational. Fouts *et al.* noted a distinct improvement in the mental attitude within 48 hours. The Cincinnati investigators did not evaluate mental symptoms.

All have noted undesirable reactions, such as sensation of heat, tingling of the skin, pruritus and dilatation of the peripheral vessels.

Dosage has varied from 60 mg. to 1 gm. daily. Fouts *et al.* gave 1 gm. daily to 1 patient and 500 mg. daily to the others. Smith, Ruffin and Smith gave 60 mg. daily either intravenously, intramuscularly or orally. The Cincinnati group has used nicotinic acid, nicotinic acid amide, and sodium nicotinate, all with similar results. They point out that the maximal and minimal dosage for oral use has not been determined, but found 500 mg. daily, divided into 5 equal doses, safe and effective in the usual case. Probably a smaller dose will be found to be effective. Intravenously, they successfully used 50 to 80 mg. daily, and 100 mg. if added to a hypodermoclysis.

All three of these reports show that nicotinic acid is effective and easily administered. Harris³⁶ with Hassan, of Cairo, treated 5 pellagrins and 3 controls with oral doses of one-third gram daily. In all 5 patients the erythema subsided rapidly and in 2 the general condition was improved. The failure of the other 3 to improve generally led him to believe that an absence of nicotinic acid may not be the sole major deficiency in some pellagra-producing diets, which leads us again to the theory of multiple deficiencies. Sydenstricker⁷⁵ has seen a relapse following complete remission with nicotinic acid and Spies, Cooper and Blankenhorn had 1 such case. Both were on deficient diets. He states that the enthusiastic reception of the drug is natural and commendable, but fears its exploitation before adequate knowledge of the essential facts is available. He continues that the present evidence strongly favors the assumption that nicotinic acid is the pellagra-preventive factor of Goldberger, but the total number of patients treated is small and the time since treatment was started is short. It is most desirable that a minimum effective dose for cure, maintenance and prevention be determined by controlled-observations of experienced investigators and that the indiscriminate use of nicotinic acid be strongly discouraged until this information is available.

It must be remembered that the evaluation of a cure for pellagra involves the maintenance of the patient on a pellagra-producing diet when the substance to be tested is administered. Such diets have been used in reported cases but such a procedure is not recommended in routine treatment. The patient is entitled to the full diet as given above with nicotinic acid used only as a supplement.

Smith, Ruffin and Smith⁶² suggest that if nicotinic acid is the pellagra-preventive vitamin, its cheapness would permit its mixture in table salt for prophylaxis in endemic areas, as iodized salt is used in goitrogenous regions. Of this Sebrell^{56c} says, "This suggestion appears to be premature because there is no information available on the effectiveness of nicotinic acid in the prevention of the disease and because so little is known about its physiologic action. It has been shown further that the diets on which pellagra develops are also deficient in other respects"—a return to the necessity for a full adequate diet.

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PEDIATRICS.

UNDER THE CHARGE OF

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MENINGITIS IN CHILDHOOD.

A REVIEW of the literature of meningitis reveals that there are many microorganismal causes other than the tubercle bacillus, the pneumococcus, the meningococcus, the streptococcus and the influenza bacillus. Some of these bacteria are of rare occurrence in meningitis but are none the less important.

Waszkoutzer⁵⁰ states that, in contrast to luetic infection of other organs, luetic meningitis is comparatively rare. Pathologically this is a diffuse or gummatous infiltration of the meninges produced by the treponema. Only in a very limited number of cases in the literature is it justifiable to speak of a leptomeningitis in the narrow sense of the word. As a rule, both soft meninges are inflamed and the underlying brain is also involved in the inflammation.

Bradford and Kelley⁷ claim that definite bacteriologic proof is offered in only a few of the reported cases of gonococcus meningitis. The organism should possess in addition to the morphologic and cultural characteristics of the gonococcus, either the proper fermentation reaction or such serologic evidence as a positive complement-fixation test or agglutination test. Of these, the characteristic fermentation test would prove the most reliable. On the same subject, Strumia and Kohlhas⁴³ state that the involvement of the nervous system by gonococcic infection appears to be rare. There are in the literature only 7 cases besides their own which are beyond question correctly diagnosed. In addition to these there have been reported as gonococcic meningitis 10 other cases in which that diagnosis is probably correct.

All proved cases of gonococcal meningitis occurred in the course of acute gonorrheal infection or during acute exacerbations of chronic gonorrheal infection.

Ravitsch and Washington³⁴ report a case of meningitis in which the *Salmonella suipestifer* was found. They state that since 1931 at the Harriet Lane Home in Baltimore there have been 28 cases of infection with this organism; but in a few the *suipestifer* infection followed some other infection, most often pneumonia. The locations of the infections were varied but in only 1 patient did meningitis occur. They found only 3 cases in the literature. In their case, because the mother had been hospitalized the previous evening with a meningococcal meningitis, antimeningococcal serum was administered intrathecally, although the smear showed no meningococci. The culture, made on admission, grew meningococci on the succeeding day and the initial blood culture grew meningococci. Spinal fluid culture made the following day was sterile, but the second blood culture showed *Salmonella suipestifer* instead of the meningococcus. On the fourth day the spinal fluid culture yielded *Salmonella suipestifer* and continued to do so for a number of days. They thought that the secondary infection with the salmonella was due to the gross contamination of the cerebrospinal fluid with blood in the course of lumbar puncture. Mitchell²⁸ reports another case of meningitis due to a salmonella bacillus. The bacteriologic report on the spinal fluid identified the organism as *Salmonella morganii*. In reviewing the literature he found only 1 report of meningitis due to this organism and this case terminated fatally. In the Mitchell case, an autogenous vaccine was administered and the infant recovered.

Kutcher²⁴ reports a case of meningitis in a child in which the spinal fluid showed *Bacillus fecalis alkaligenes*. His search of the literature for a previous case met with no success. He presents this case because of its rarity and as an addition to the rather limited list of organisms of the Gram-negative group which cause meningitis. The organism was described by W. D. Booker, in 1886, and was recovered by him from a case of cholera infantum. It was a Gram-negative motile bacillus possessing cultural characteristics peculiar to itself. This organism was demonstrated in Kutcher's case of meningitis. Kutcher says that probably every bacterium that is capable of producing general septicemia has at one time or another been found responsible for a case of meningitis. According to him, the more commonly found Gram-negative bacilli include influenza, Koch-Weeks, Morax-Axenfeld, pertussis, Ducrey's tularemia, coli group, cloacae, lactis aerogenes group, dysentery group, Friedländer's group, typhoid group, chromogenic group, alkaligenes and melitensis.

Black⁴ reports a case of meningitis in an infant of 4 months in whom the diagnosis of *Brucella melitensis* meningitis was made by postmortem examination. He points out that two main modes of transmission of *Brucella* infection to man are recognized. One of these is by the ingestion of infected dairy products such as raw milk, cream and butter. The other is by the handling of infected livestock, infected tissues or uncooked meats. In his report he does not indicate the manner in which his patient may have become infected. Poston and Thomason³² also report a case of meningitis due to *Brucella melitensis*.

Craig and Mackenzie¹⁰ report a case of meningitis due to *Bacillus acidi lactici*, because of its rarity. They say that there have been only 4 previous reports in the literature, 2 being in new-born infants, 1 in a premature infant at the age of 1 month and 1 in an adult. Incidentally they found only 5 references to this infection in other parts of the body. This is a Gram-negative bacillus belonging to the colon bacillus group. It is found in the intestinal canal and is considered to be a harmless saprophyte without pathogenic significance. It may be found in water and in milk. In discussing the possible modes of entry of organisms into the intracranial cavity the authors enumerate several avenues. One possibility is that of intrauterine transmission from the mother in those cases in which there is a prenatal meningitis or one which occurs during the first days of life. Another source of infection is from an otitis media. Still another atrium is through the lymphatics or by direct extension from a contiguous focus in the nose or the mouth. Premature respirations with aspiration of contaminated amniotic fluid and subsequent passage through the Eustachian tube is another possible source of infection. Finally, the infection may be milk-borne.

Another rare type of meningitic infection was reported by Poston, Upchurch and Booth.³³ In this report of a child with clinical symptoms of meningitis, no bacteriologic diagnosis was possible from the spinal fluid, but on necropsy, material from a subdural abscess gave a Gram-positive bacillus which produced beta hemolysis on blood agar. Morphologically and culturally this organism resembled the new species of *listerella*.

Meningitis is frequently a secondary condition complicating some other primary infection. In the recent literature, there are several reports of this occurring as a complication of several of the infectious diseases of childhood. Gordon, Litvak and Caronna³⁰ report 2 cases of streptococcic meningitis, and 1 of sympathetic meningitis accompanying streptococcic abscess of the brain complicating scarlet fever. They say that acute purulent meningitis with scarlet fever may be primary or secondary. The primary type is restricted to instances in which careful search during life or at postmortem fails to reveal any localized source of infection. This is exceedingly rare. It may be even rarer than the literature would indicate, since involvement of the middle ear, sinuses or mastoids which failed to give clinical signs during life may be observed at postmortem examination. The pathways of invasion of the meninges in primary meningitis are through the nasopharynx and along the olfactory filaments by way of the cribriform plate of the ethmoid bone; through the sphenoid sinuses to the meninges; by way of the blood stream or lymphatics, and, according to some observers, through the choroid plexus with the current of fluid that is constantly flowing through the foramina of Luschka and Magendie into the subarachnoid space. Secondary purulent meningitis is usually associated with some localized infection. The channels of invasion of the meninges in this type of meningitis may be through the labyrinth or the tegmen tympani. The infection may also travel by way of the local lymphatics or blood capillaries without any visible continuity between the inflammatory focus and the meninges.

Carlson and Morgan⁵ report a case of diphtheritic meningitis and

in a search of the English literature were unable to find such a case, although there were 4 cases found in the German literature. Their case developed following otitis media and mastoid. Klebs-Loeffler bacilli were found in nose and throat cultures and in smears from the spinal fluid.

Faust¹³ states that neurologic complications of the common contagious diseases, although only occasionally seen in practice, are not rare. The majority of such complications occur in measles, German measles and mumps. In chicken-pox, they are a much less frequent complication. He reports such a case.

A form of meningitis is encountered in the current literature which is a clinical entity of rather recent recognition. This is called acute lymphocytic meningitis. Viets and Warren⁴⁹ say that acute lymphocytic meningitis, now classed as a specific virus disease, may be transient or severe and prolonged, or even fatal. They report examples of all three types. According to their findings, the disease in its most severe form is an encephalitis as well as a meningitis. With the high recovery rate it must be assumed that the degree of encephalitis, in the majority of cases that have been reported, is not profound and that the clinical designation of acute lymphocytic meningitis is still justified.

Toomey⁴⁶ describes an epidemic of a disease, the symptoms of which are excruciating headache; anorexia with nausea or vomiting or both; pain in the epigastrium on palpation; a low-grade fever; a throat moderately or severely inflamed; some pain on movement of the head; a total white count perhaps lower than usual, but if normal, usually with a relative increase in the circulatory lymphocytes; negative neurologic signs; a spinal fluid pleocytosis with lymphocytes predominating in the severely affected cases; and a hemolytic streptococcus that was easily isolated from the throats of a small percentage of the cases. He thinks that the lack of glandular involvement, the finding of spinal fluid pleocytosis and the changes in the blood picture are distinctive enough to classify this as a new syndrome and he terms it acute epidemic lymphocytosis.

Baird and Rivers² present 65 cases which indicate that not all instances of acute aseptic meningitis are due to the virus of lymphocytic choriomeningitis. The etiologic agent or agents responsible for the cases not so induced are not known. From the records of 3 of the cases of lymphocytic choriomeningitis it seems that certain cases of the disease, because of the extent of the paralysis and sequelæ, do not satisfy the criteria laid down for the diagnosis of acute aseptic meningitis. It is difficult or impossible to differentiate by clinical means alone the cases of acute aseptic meningitis caused by the virus of lymphocytic choriomeningitis from those not produced by this agent. However, the spinal fluid cell counts in the cases studied tend to be higher in the former group than in the latter. Livierato and Simoneto²⁷ observed 5 patients in whom the clinical picture resembled that of tuberculous meningitis. They report that the duration of the disease varied from 14 to 28 days. The subjective and objective symptoms were temporarily improved by lumbar puncture. All of the patients made complete recovery without residual signs in the nervous system. The cerebrospinal fluid was negative bacteriologically and guinea-pig inoculation for tubercle bacilli also gave negative results. The most

remarkable result of the examination of the spinal fluid was the discrepancy between the number of white cells and the quantity of albumin. The lymphocytes were markedly increased, with a tendency to further progression in this direction, while the albumin was either normal or only slightly increased. Blood cultures and examination of the blood for malaria were negative. Intracranial injection of cerebrospinal fluid into dogs and rabbits gave negative results. Because of these points the authors believe that the disease lies in the class of meningitis close to that of poliomyelitis or epidemic encephalitis.

Dummer, Lyon and Stevenson¹² report their observation in a group of 22 cases manifesting symptoms of benign lymphocytic meningitis. The peak of this small epidemic occurred in the months of July and August. The disease developed in widely separated areas of the community except in 2 instances, so that contact with known patients could not have been responsible for its spread. The characteristic symptoms of the disease were headache, vomiting and abdominal pain. On physical examination, rigidity of the neck and positive Kernig and Brudzinski signs were most frequent. Most of the cerebrospinal fluids contained from 50 to 200 cells, chiefly lymphocytes, and the globulin content was *greater than normal in about one-half of the group*. The fever was of short duration, and in 19 of the 22 cases the leukocytes of the blood were not increased above normal figures. Recovery was rapid and complete. More than one-half of the group were examined from 6 to 8 months after recovery from the disease but no evidence of residual symptoms and signs, nor of changes in behavior, could be discovered. The mildness of the infection, its epidemic characteristics and the absence of any other disease in the patients or in the community makes the observers suspect that this was a definite disease entity probably of a virus nature.

Noone, Habel and Riggs³⁰ report 37 cases of epidemic lymphocytic meningo-encephalitis in which there was rapid and uneventful recovery in 36 cases. One patient died. There were headache, fever and vomiting in practically every case. Headache was the most striking symptom. In the spinal fluid examinations, the total cell counts varied so widely that it was impracticable to attempt to average them. The range of cell counts was from 40 to 650 cells. The cells were chiefly lymphocytes.

Glanzmann and Heller¹⁸ point out that there are entirely benign serous and even suppurating meningitides, and for this reason it is advisable to be cautious in rendering an unfavorable prognosis in cases presenting meningitic symptoms. The onset is acute and the spinal fluid shows meningitic changes in that there is an increase in the mononuclear cell elements while the fluid may remain clear as is the case in serous meningitis, or there may be a noticeable suppurative turbidity. Direct examination as well as cultures may reveal that the spinal fluid is sterile. This is known as aseptic meningitis. The course is relatively short, benign and without secondary complications. Etiologic factors in the form of local disorders such as otitis media, sinusitis, pneumonia, and intoxication may be absent. There may be no systemic disease or acute or chronic infection as the cause. This form, according to the authors, develops chiefly in children and occasionally even in nurslings.

Staphylococcus as the cause of meningitis is extremely rare. Bloch and Pacella⁶ report a case in a child of 17 days. This was interesting, as the occurrence of staphylococcal meningitis under 1 month of age is very uncommon. The baby had a meningocoele in the occipital region which was removed when the infant was 6 days old. The symptoms of his illness appeared 2 days later. Under a scab at the site of the meningocoele, thick pus was encountered and showed many Gram-positive cocci in clusters. The patient recovered under sulphanilamide treatment.

Speaking of influenzal meningitis, Huntington and Wilkes-Weiss²³ point out that, according to the usual concept, influenzal meningitis is usually primary. In 10 of their cases it seemed clear that the onset of meningitis was preceded by otitis media or pneumonia, and in some additional instances there were other features of interest in the recent history. In the remaining 40 cases, the meningitis might be considered primary, although many of the patients had concomitant otitis and pneumonia. As regards the diagnosis, the authors emphasize the fact that the presence of Gram-negative bacilli in the spinal fluid is not sufficient, but the diagnosis should be confirmed by culture of the spinal fluid in every instance. In purulent intracranial infection in young children the conventional signs are often absent, and influenzal meningitis is no exception to this rule. Suspicion of meningitis in any unexplained febrile illness of an infant is most justifiable. Extrameningeal lesions such as abscess, pleural effusions, pericarditis, metastatic lesions, osteomyelitis, cellulitis and purpura should be looked for. Either leukocytosis or leukopenia may be present in the case of meningitis. The authors found *H. influenza* in one or more cultures in 16 of 24 blood cultures. Fothergill¹⁵ states that, although *H. influenza* meningitis is supposed to be a rare disease, this is only true in the case of adults. Another point that he brings out is that the mortality rate is very high, being 98% in untreated cases. For the treatment of this infection an antiserum has been produced by the immunization of horses with virulent meningococcal strains of *H. influenza*. The serum is given intravenously once a day for the first 2 days in dosages of 30 cc. for an infant and from 30 to 50 cc. for older children. The usual precautions against anaphylactic shock must be taken. It is necessary to give the serum intravenously in order to overcome the bacteremia which is present. However, this means of introducing the serum is of little or no value in treating the infection in the subarachnoid space because of the very slight permeability of the meningeovascular barrier for antibodies. For this, a mixture of antiserum and complement is given intrathecally twice a day as long as it seems necessary. The mixture consists of 2 parts of antiserum and 1 part of complement, and the usual dose is 15 cc. of the former and 8 cc. of the latter. It is allowed to run in by gravity after the spinal fluid has been completely drained off. However, the amount of the mixture injected must be less than the quantity of spinal fluid withdrawn. It is important to elevate the foot of the bed after each intrathecal administration and the position of the patient should be changed frequently in order to facilitate the distribution of the mixture throughout the subarachnoid space. While these injections are usually given by lumbar puncture, they may be injected into the lateral ventricles. More on the same

subject has been reported by Huntington and Wilkes-Weiss,^{23b} Silverthorne, Fraser and Snelling,⁴⁰ Taylor,⁴⁴ Spekter⁴¹ and others.

In reporting a case of pneumococcus meningitis that recovered, Bennett and Meier³ comment that meningitis of this type has an exceedingly high mortality rate and this is particularly true where it complicates otitic infection. Since 1896 until the time of this report some 50 cases of recovery have been recorded, but before the earlier date there has been no recoveries. The treatment of these reported cases of recovery has been variable, but the majority of them have been treated with pneumococcal serums, intraspinally and intravenously. While this was all that was done in some cases, other treatment was given in other cases. These include injections of gentian violet, Pregl's solution, mercurochrome, autogenous vaccines and urotropin by mouth. Optochin has been used with some success.

Shuller³⁸ says that pneumococcic meningitis is a disease caused by the pneumococcus and may be primary in the meninges or may be secondary to a pneumococcic infection in some distant organ. Pneumococcic meningitis may present the typical symptoms of any meningitis, or it may be practically devoid of any nervous symptoms. The diagnosis of this type of meningitis depends on the symptoms and upon the evidence obtainable from the spinal fluid. The Gram-positive organism is not always found on the first puncture. In several reports specific type pneumococci were identified. Weil⁵¹ reports a case of meningitis due to Type I pneumococcus which was treated with specific type serum and recovered. Frankmann and Stewart¹⁶ report a case of Type II pneumococcus meningitis which recovered and the authors attribute the recovery to hyperthermia. The hyperpyrexia resulted from the reaction to the infection in the ear and mastoid with which the meningitis was associated. Meningitis caused by Type III pneumococcus resulting in recovery is reported by Steinhilz.⁴² Hirsch²¹ reports a case of primary meningitis due to Type XXII pneumococcus. Coppolino and Gannone⁹ report a case of pneumococcic meningitis in 2-day-old infant.

Meningitis due to streptococci is quite common, as will be shown, but the non-hemolytic streptococcus occurs infrequently as the etiologic factor. Hodges²² reports such a case in which there was also congenital heart disease. It may have been that a septic embolus was thrown off from a thrombus superimposed on the congenital heart lesion. At postmortem, careful search of the endocardium failed to show thrombus, vegetation or scar. It may have spread from infection in the left middle ear. This does not seem likely, as there was no evidence of such involvement, and at postmortem the process was acute and apparently recent. It may have resulted from a blood stream infection from some other source. There was an acute febrile attack with sore throat, back pain and rash some 11 days before the onset of meningeal symptoms and this may have been the source of the infection. Scott and Radbill³⁷ say that while streptococcic meningitis is a fairly common disease, only a few recoveries are recorded annually. They report a case which complicated mastoiditis. Recovery followed mastoidectomy, the usual supportive treatment and the administration of lyophile convalescent scarlet fever serum intrathecally. Zeligs⁵⁴ records 2 cases of streptococcic meningitis in which

there was recovery. He feels that the most important factor in the treatment of meningitis is to provide adequate drainage. In 1 of his cases there was spontaneous drainage of spinal fluid from the nose as a result of a fracture of the skull. In the other, daily injections of air not only removed the intraspinal block and prevented new blocks from forming, but it also displaced fluid from the ventricles and materially aided drainage.

Schillinger³⁵ feels that the treatment of streptococcic meningitis, which is usually otitic, should be prevention. Each case of otitis should be considered as a potential case of meningitis. In that way extension of the infection can be promptly recognized. Such cases should be relieved of the focus of infection by free surgical drainage when they evidence irritation of the dura or invasion of the blood stream. Furlow and Reynolds¹⁷ describe their method of continuous early drainage of the subarachnoid space by means of a ureteral catheter. In conjunction with this they administer large quantities of fluid.

Litvak and Klughertz²⁶ express several reasons for the marked increase in recovered cases in recent years from streptococcic meningitis. The early diagnosis of otitic meningitis and early and complete eradication of the macroscopic and microscopic foci of infection is the first reason. Next are improved methods of treatment, such as concentrated scarlet fever antitoxin and sulphanilamide and its derivatives. The beneficial results of the use of the various forms of sulphanilamide in streptococcic meningitis are reported by a number of authors, including Trachsler, Frauchenberger, Wagner and Mitchell,⁴⁷ Anderson,¹ and Godwin.¹⁹

Blacklock and Griffin⁶ say⁴ that tuberculous meningitis is the most frequent form of meningitis in children. The primary site of infection in a series of 241 cases under 13 years of age was most frequently thoracic in 73.9%, abdominal in 22.8%, in the cervical glands in 2.1% and unknown in 1.2%. Meningitis following primary thoracic lesions was nearly always due to the human type of bacillus and that following primary abdominal lesions was usually due to the bovine type. According to Turner⁴⁸ 5% of patients who die of tuberculosis present a meningeal form of the disease and this is especially true in extrapulmonary infections. Scott³⁶ states that in 300 autopsies, excluding 9 cases in which brain tuberculomas were found, the meninges showed tubercles in 93 of 225 children less than 10 years of age. Between the ages of 10 and 20 there were 3 among 10, leaving 32 among 65 adults more than 20 years of age. Peterman and Kohn³¹ say that it is the almost unanimous opinion that tuberculous meningitis is the most common type of meningitis. From a study of 47 definitely proven cases they found that tuberculous meningitis ranks next in frequency after meningococcic meningitis. The first symptoms to appear were vomiting, change in disposition, anorexia, cough and fever. The cases all terminated fatally and most of them in the third week. It was possible to find tubercle bacilli in the spinal fluid in 78% of the entire series and 91% of the recent series in which a special study of the spinal fluid was done. The Levinson test is recommended as an extremely valuable aid in diagnosis. It was found positive in 82% of the cases.

The meningococcus is conceded first place as the causative factor of meningitis. The literature is filled with reports and studies of this

infection. The frequency of this disease especially in epidemics has stimulated investigations into the occurrence of this organism in the nasopharynx of normal individuals. Silverthorne³⁹ states that in epidemics high contact carrier rates have been shown. Carriers have also been found during interepidemic periods. In his own study, he found in 1227 swabs from 63 normal healthy adults over a 2-year period 19.8% positive for meningococcus. The swabs were made at practically monthly periods. On these monthly examinations the number of positive individuals varied from 16 to 28%. No less than 41% of the group of 63 were positive at one time or another during the 2-year period. Eleven individuals were persistent, 13 were intermittent and 2 were transient carriers. He examined 11 non-contact carrier strains by the bactericidal and mouse-mucin tests and found 3 to be virulent and 8 avirulent. Carriers of meningococcus possess bactericidal power in their blood to their respective strains, whether these strains are virulent or avirulent. Samples of blood from carriers possess bactericidal power to certain virulent cerebrospinal fluid strains.

Craster and Simon¹¹ state that a thorough knowledge of the bacteriology, anatomy and physiology of the meninges and the cerebrospinal fluid is essential for the proper early diagnosis and treatment of meningococcus infections, which have a low incidence rate and a high mortality rate. A petechial or purpuric rash may be considered the specific rash of meningococcemia. A purpuric rash accompanies the petechial rash when the condition is fulminating. The rash occurs before the spinal fluid becomes cloudy and before the meningeal signs appear. In many cases meningococci may be demonstrated by a Gram stain of blood obtained by needle puncture of a petechial or purpuric area. A Wright stain of blood from a non-purpuric skin may also demonstrate meningococci. Acute fulminating meningococcemia associated with adrenal hemorrhage is called the Waterhouse-Friderichsen syndrome. In infancy, especially in the first and second years of life, the early signs of meningococcal infection of the meninges do not point to involvement of the central nervous system. They are more likely to suggest an infection of the upper respiratory tract or a gastrointestinal disturbance. After the disease is well established the stiff neck, the Kernig and Brudzinski signs and other meningeal signs appear.

Levy and Litvak²⁵ review the findings from a study of 36 cases of meningococcal meningitis. They say that much has been said of permanent damage to the spinal cord and the intervertebral cartilages by lumbar puncture, but they feel that this hazard is small compared with that of a delay in the treatment of a case of meningitis. If there is a reasonable possibility of central nervous system involvement, lumbar puncture should be performed. If the fluid is clear it does not always preclude the possibility of meningitis. The fluid should always be examined carefully. A smear and cell count should be done, a culture prepared and test made for albumin, globulin and sugar. The rule still holds that antimeningococcal serum should be given immediately if a cloudy spinal fluid is obtained. The serum should always be kept in readiness when a lumbar puncture is done in any suspected case. The infants and younger children seldom demonstrate the classical meningeal symptoms and signs. This point cannot be overemphasized. Sometimes meningococci are difficult to culture. Ferry¹⁴ says

that the meningococcus produces a soluble toxin, specific to the various types of the organism, which stimulates the production of homologous antitoxin in susceptible animals. Neutralization of the toxin takes place *in vivo* as well as *in vitro*. Recovery from meningococcal meningitis follows intravenous injections of the antitoxin irrespective of the invasiveness of the organism.

Another new idea in treatment of meningococcal meningitis is recommended by Thompson.⁴⁵ This is continuous spinal drainage. While it is physiologically sound it has not gained widespread use because of the technical difficulties. It is most suited for the treatment of meningococcal meningitis where the pus does not tend to become too thick to pass through a cannula as it frequently does in streptococcal and pneumococcal meningitis.

Neal and Appelbaum²⁹ say that their results with sulphanilamide in meningitis due to the hemolytic streptococcus have been excellent and in pneumococcal meningitis encouraging. Their experience in meningococcal meningitis was too limited for definite conclusions to be drawn, but it is their impression that it is of value in this type of infection. Willien⁵³ states that the clinical response of the patients to treatment with sulphanilamide was satisfactory in every case in his experience. The possibility of being able to cure meningococcal meningitis by the administration of sulphanilamide by mouth only will be of untold benefit by eliminating the time, trouble and expense of intraspinal and intravenous therapy, together with the elimination of the danger of protein shock and the discomfort of serum sickness. His routine of administration was an initial subcutaneous injection of a large dose of the saturated 0.8% solution in amounts approximating 0.05 gm. per kg. The drug is administered by mouth every 4 hours day and night. The dosage is graduated downward from an upper limit of 15 grains every 4 hours, depending on the size of the patient and the severity of the infection. The drug is continued in reduced dosage for about 10 days after symptoms and laboratory readings have returned to normal. The reason of this is because the drug is bacteriostatic rather than bactericidal. Sodium bicarbonate is recommended grain for grain with sulphanilamide in order to combat acidosis. Magnesium sulphate or sodium sulphate and even sodium chloride are avoided in order to prevent sulphhemoglobinemia.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MAY 16, 1938

A Simple Method for the Determination of Mucin in Gastric Secretion.
 HARRY M. EBERHARD and CHARLES W. SCHAFFER (Hahnemann Medical College and Hospital, Philadelphia). While doing fractional gastric analyses and duodeno-biliary drainages, one of us has noticed, after examining the samples of saliva recovered during these examinations, that the mucous content of the saliva was totally different from that noted in the gastric juice, bile, feces and so forth. Routine examination of the saliva and other samples by the older methods were too time consuming, so a simpler and more rapid method has been evolved.

The methods generally used and published for the determination of secreted mucin were found lengthy and tedious; extensive investigation with many organic solvents was conducted and it was found that the chlorhydrins were the only water-soluble organic solvents in which mucin at its iso-electric point (pH 3.5) was totally insoluble and readily precipitated.

Pepsin and other proteins of the gastric secretions are not precipitated and are soluble even in the presence of excess chlorides which do not affect the precipitation of mucin. The procedure is simple.

To free it of food particles that are undigested, the sample of gastric contents is filtered through cotton placed loosely in a funnel. To 10 cc. of the gastric secretion are added 20 cc. of ethylene chlorhydrin; shake or agitate to mix thoroughly the chlorhydrin. The mixture is then brought to pH 3.5 by the addition of HCl or NaOH and allowed to stand for about 30 minutes; at the end of this time the mucin is quantitatively precipitated. It may be filtered off and washed on the filter with 65% ethylene chlorhydrin (pH 3.5), dried and weighed; or the pH standardized chlorhydrin solution may be put into a graduated cylinder and the quantity of mucin read directly.

On our graduated "mucinometer" each line represents 10 mg. of mucin. This mucinometer is similar in principle to the albuminometer in which the precipitated protein is read in mg. per cc. volume.

The entire procedure takes 1 hour as against 16 to 18 hours by the ethyl alcohol precipitation, protein hydrolysis and glucose titration method.

We have found that any of the chlorhydrins may be used successfully, but that the ethylene chlorhydrin precipitated the mucin more rapidly. Temperatures of 20° to 25° C. were found most favorable.

Quantitative Emission Spectrum Analysis of Gastric Juice and Allied Problems. A. N. LUCIAN (Randal Morgan Laboratory of Physics, University of Pennsylvania). In this paper were presented the following phases of the subject of spectrum analysis:

1. The advantages presented by quantitative spectrum analysis. Among these were enumerated the following:

(a) Very great sensitivity. It was reported that amounts less than 0.000,001% in quantities of the order of a gram were easily detected.

(b) Very small quantities are needed for specimens. Liquid specimens of the order of 0.05 to 0.1 cc. were sufficient for analysis.

(c) With improved technique, precision of 5% or better can be expected.

(d) Many different elements can be determined simultaneously regardless of the dissimilarity of their chemical properties.

2. A discussion of the fundamental physical analysis by the emission spectrum was given. The significance of the *ultimate* or *persistent* lines was brought out.

Brief mention was made of the two well-known standard methods:

(a) The step by step comparison method of de Gramont.

(b) The internal line standard of Gerlach and Schweitzer. Then a brief discussion of the improved method developed by the author was given. This consisted of obtaining a standard curve for each element (which in all cases so far tried is a straight line) by plotting the density values of the spectrum line or lines of the element, produced by a series of standard solutions, against the known concentrations of the element in question in the various standard solutions, and from such curves reading off the actual amount of the element in question in the unknown samples.

3. A preliminary report of the results obtained was given.

A large number of specimens of fasting gastric juice were obtained under carefully controlled conditions, to minimize the chances of contamination.*

The elements identified in all the specimens were the following: Na, K, Ca, Mg, P, Fe, Cu, Zn, Pb, Mn and C. Other elements were occasionally encountered, notably Sr, Al, and Si.

Referring to the above-mentioned 10 elements (not including C), the following table shows the extreme values of the concentration of these elements ever found in gastric juice specimens investigated in this work.

	Mg. per 100 cc.		Mg. per 100 cc.
Na	53.00-141.0	Cu	0.120-1.80
K	48.00-125.0	Zn	0.150-0.78
Ca	3.00- 19.5	Pb	0.000-0.09
Mg	0.75- 3.5	Fe	0.020-0.10
P	5.80- 13.0	Mn	0.002-0.03

An attempt was made to study the variation in the concentration of a given element with the change in the pH value of gastric juice. As a preliminary report it was stated that as far as the alkali metals, Na, K and Ca, are concerned no definite and consistent trend was noticeable. In contrast, some of the other metals, notably Cu, showed what appears to be a definite trend. A plotted curve indicates that the concentration of copper decreases with increasing values of pH. Further conclusions with regard to this point (concentration vs. pH) must await further careful measurements.

Differences Between Castration Cells and Thyroidectomy Cells of the Rat Pituitary in Response to the Administration of Oestrone and of Thyroid Extract. ISOLDE T. ZECKWER (Laboratory of Pathology, University of Pennsylvania). Rats were operated upon at 5 weeks of age and killed 5 weeks later. In each group, some were injected daily with oestrone during the entire postoperative period, the total dosage varying up to 2900 I.U. Others in each group were fed desiccated thyroid extract daily, during the entire postoperative period, the total dosage varying up to 2 gm. The histologic appearance of pituitaries of the treated rats was compared with that of untreated rats. Ninety-four pituitaries were studied.

Complete thyroidectomy was evidenced by characteristic stunting of skeletal growth and inhibition of kidney growth. The effect of oestrone was obvious in the characteristic effects on the gonads. In spite of the known diffuse effects of oestrone in degranulating all chromophile cells, whether the dosage of oestrone was large or small, thyroidectomy cells were abundant in the pituitaries of all thyroidectomized rats. Adequacy of oestrone dosage was proved by its characteristic effect in preventing castration cells in both male and female gonadectomized rats.

The feeding of thyroid extract had no effect on the castration changes in the pituitary when given in doses far in excess of that necessary to prevent the development of thyroidectomy cells in the thyroidectomized rats.

* These specimens were supplied by Drs. Harry Shay and J. G. Cohen of the S. S. Fels Foundation, where this work was carried out.

It is concluded that castration cells and thyroidectomy cells are histologically and functionally different cells, whether or not they arise from different or identical precursor cells.

The Synaptic Excitation of Nerve Cells. D. W. BRONK, M. G. LARABEE, and J. B. GAYLOR (Eldridge Reeves Jolinson Foundation, University of Pennsylvania). Because the frequency of nerve impulses largely determines their effects, it is important to know how that frequency is modified when the impulses cross a synapse. Recording the response in one or a very few postganglionic fibers (from stellate of cat) while stimulating the preganglionic nerve, we have shown that when the impulses arrive at frequencies corresponding to those which normally occur in the organism, each presynaptic impulse initiates only one postsynaptic impulse.

If, however, the impulses arrive at higher frequencies, there is no longer one synchronized volley of postganglionic impulses for each preganglionic volley. Furthermore, the ganglion cells continue active for some seconds after the end of preganglionic stimulation. Evidence is thus provided for the first time showing conclusively that a train of impulses arriving at a synapse may set up an excitatory state which persists for long duration at a level sufficient to stimulate.

The dependence of synaptic transmission on blood supply has been studied in a perfused ganglion. Certain pathways cease to transmit about 10 minutes after arresting the circulation; all cease to function within 30 to 45 minutes. Recovery has been observed when the circulation is restarted after $7\frac{1}{2}$ hours. The determination of relative rates of failure of conduction over synaptic and purely axonal pathways shows that the synapse does not fail more rapidly than the axon. When conduction is blocked by anemia, the postganglionic cells can no longer be excited by perfusion with acetylcholin. From this, we conclude that loss of irritability of the cell body fails as soon as, if not sooner, than any other part of the synaptic region.

Further Studies on the Mechanism of Kaolin Hypertension. E. ROBERTS and J. Q. GRIFFITH, JR. (Robinette Foundation, University of Pennsylvania). This material is a study of hypertension produced in rats by the intracisternal injection of 0.04 cc. of a 25% suspension of kaolin. Following the intracisternal injection in the rat, vascular hypertension occurs by the fifth to twelfth day and pressure tends to fall to normal by the third month. There is increased cerebrospinal pressure. Internal communicating hydrocephalus frequently, though not invariably, occurs in animals surviving a month or more. There is impairment of perineural absorption from the cerebrospinal space into the lymph system but no alteration of absorption into the blood stream. There probably is block in the perivascular spaces leading to the surface of the cortex which may be a factor in the production of hydrocephalus. In long-standing cases the gray matter of the cortex is thinned out of proportion to that seen in another form of hydrocephalus due to cerebellar tumor. Water content of the brain is normal. Blood volume is normal. Minute vessel pressure is increased but falls

in the flare area of a burn. Mean pressure and systolic pressure are both elevated. This hypertension can occur following complete bilateral adrenalectomy. The carotid sinus responds normally to electrical stimulation.

Correction. The statement under "Dosage of the Drug" (AM. J. MED. SCI., 195, 708, 1938) which read: "In general we have usually given as an initial dose 0.6 gm. per kilo of body weight" should be changed to read: "In general we have usually given as an initial dose 0.06 gm. per kilo of body weight."

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THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

AUGUST, 1938

ORIGINAL ARTICLES.

THE UNITED STATES ARMY'S WAR IN THE AIR AGAINST THE
MOSQUITO-BORNE DISEASES.*

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OUR war in the air rarely makes the front page of the newspaper; nevertheless it is a major conflict, which began half a century ago and is still being waged on many fronts at home and abroad. For the benefit of any pacifistic friends who may be present I hasten to add that this is a war of defense. It has been fought, not with airplanes and high explosives, but with test-tubes and steam shovels, microscopes and Paris green, quinine cocktails, and native battalions, clearing the muck from jungle swamps. In other words, my title refers to the fight of the Medical Corps against the mosquito-borne diseases.

As this fight is a part of the campaign waged against all infectious diseases, I will digress a moment to indicate some of the purposes of this broader campaign. The primary objective of the Medical Corps is to safeguard the health of the soldier and keep him physically fit, especially during periods of national emergency. In the attempt to accomplish this, the civil profession has always been called on for help. The best available medical and surgical care has been given the sick and wounded, and every effort has been made to prevent infectious diseases. Both of these activities are essential, but the latter is more important to the conservation of man power.

Throughout history, epidemics have been the scourge of armies operating in the field, and prior to the development of modern pre-

* Read at a meeting of the Undergraduate Medical Association of the University of Pennsylvania, Philadelphia, Pa., December 7, 1937.

ventive medicine, the infectious diseases consistently caused more disability and death than did battle injuries. In fact, they frequently decided the outcome of important wars.

Considerable progress has been made in the attempt to protect the soldier, but much remains to be done. During our various wars of the past the following proportions of the total deaths were caused by disease:^{1,43} Revolutionary War, 90%; Mexican War, 84%; Civil War, 62%; Spanish American War, 87%; and World War, 50%. In the Civil War, disease was responsible for more than 224,000 deaths in the Union force of 2 million men; on the other hand, during the World War there were only 50,000 disease deaths in our army of 4 million men. In the latter conflict, the respiratory infections predominated, and for these we still have no satisfactory methods of control. The prevalence of the intestinal group of diseases was relatively low, and typhoid was unimportant due to improvements in field sanitation and the use of "triple-typhoid" vaccine. Smallpox was eliminated by vaccination. Certain other important infections caused little or no trouble, but only because they were not endemic in the regions occupied by our troops. The latter group included some of the diseases transmitted by mosquitoes.²²

The army's struggle against mosquito-borne diseases began under the leadership of G. M. Sternberg, a pioneer scientist, who was referred to by Robert Koch as the "Father of American Bacteriology."^{25,41} In 1916, your A. C. Abbott paid tribute to Sternberg's influence on the development of preventive medicine in this country and expressed appreciation of his good fortune at having served as assistant to this able man.

Sternberg entered the army during the Civil War, and served with distinction on many battlefields. Early experiences with epidemics of typhoid, cholera, yellow fever and malaria created in him an intense interest in the then young science of bacteriology, and a life-long desire to prevent the military plagues. In 1880, his translation of Magnin's book on bacteriology constituted the first American text on this subject, followed in 1892 by his own more extensive "Manual of Bacteriology." During his long service he had several opportunities to investigate yellow fever, and by careful bacteriologic studies he disproved the claims of various workers who believed they had discovered the causative agent. In 1881, he refuted the claims made for the "Klebs-Tommasi-Crudilli" bacillus as the cause of malaria; and 4 years later, at Johns Hopkins University, he demonstrated for the first time in America, the living plasmodium of malaria. During the period from 1893 to 1902 Sternberg's duties as Surgeon General of the United States Army, interfered with his personal laboratory investigations, but afforded opportunity to develop in the Army his ideas concerning the importance of experimental studies in dealing with military diseases. At an early period he established the Army Medical School, organized laboratories in

army hospitals, and in every way possible stressed the importance of medical research.

After the Spanish American War, General Sternberg ordered the formation of special boards of officers for the investigation of the important diseases in our newly acquired tropical possessions. Major Walter Reed and his associates were sent to Cuba, where they discovered the mosquito transmission of yellow fever. Lieut. B. K. Ashford proved that the malignant disease, "Puerto-Rican" anemia, was due to massive hookworm infection, and began a campaign of control, which was the forerunner of the world-wide eradication program of the Rockefeller Foundation. The third board was established in the Philippine Islands under Lieut. R. P. Strong, now of the Harvard Medical School, and he, and those who succeeded him, contributed to our knowledge of various diseases, including dysentery, plague, beri-beri, filariasis, surra, malaria, and dengue fever.¹⁷ This latter board existed in Manila until 1934, when it was transferred to Ancon, Panama Canal Zone, where its members are now engaged in the study of malaria and other important diseases. Many of these tropical infections are of relatively slight importance to the army under present conditions, but some are potentially dangerous, and might seriously cripple a military force required to operate in regions where they are prevalent. This applies particularly to yellow fever, dengue fever and malaria.

Yellow Fever. Yellow fever has existed in the American tropics for at least 4 centuries, and during the past it has frequently invaded the temperate regions in the summer months. It is rarely severe among the adult natives of endemic areas apparently because a large proportion of such individuals become immunized through mild, childhood infection. However, among non-immune adults, either visitors from abroad or the inhabitants of newly invaded regions, it may cause explosive epidemics with high morbidity and mortality.

Before the present century, destructive outbreaks of yellow fever were frequent among European troops operating in the West Indies and in South and Central America. A spectacular example occurred during the revolt of the blacks in Haiti, when a veteran French Army was practically annihilated.¹ In 1802, a force of 58,545 troops embarked at Brest for Santo-Domingo, and within 4 months 50,270 were dead, chiefly of yellow fever. Of the 8000 remaining 3000 were sick or wounded. In 1809, this army was reduced to 300 men, who returned to France. In the United States alone there have been more than 100 epidemics. Most of these occurred in the South; but on many occasions yellow fever appeared in our northern cities, including Philadelphia, New York, and Boston; and even invaded Canada. It is estimated that the disease caused at least 100,000 deaths in this country. During the brief war with Spain, 1300 cases of yellow fever occurred in our troops, and caused 200 deaths.

In 1900, Walter Reed went to Cuba with instructions to investigate yellow fever and to determine the etiologic significance of Sanarelli's *Bacillus icteroides*. The bacillus was soon ruled out, and Reed's well known human experiments were begun, to test Dr. Carlos Finlay's²⁴ belief in the mosquito transmission of yellow fever. After 12 months of heroic work it was proved that the disease is transmissible by *Aedes aegypti* and the mechanism of its transmission was determined.²⁶ This information was immediately applied by the Governor of Cuba, General Leonard Wood, who ordered an intensive campaign against mosquitoes, which was effectively carried out by Colonel William Gorgas. By 1902, the city of Havana which had been cursed with yellow fever for more than 150 years, was for the first time free of this disease. Similar control work was soon done elsewhere, and within a few years the United States, the Panama Canal Zone, and many tropical regions were likewise released from the yoke of yellow fever.

By 1914, it appeared that the disease had been eliminated in all but a few endemic foci, including one in Ecuador and possibly others in Mexico and West Africa. Acting on the advice of General Gorgas, the Rockefeller International Health Board therefore undertook a campaign which had as its purpose the eradication of yellow fever from the face of the earth. In 1918, a commission was sent to Guayaquil, and after 6 months of *Aedes* control work, the disease disappeared from that region. Incidentally, it was here that Noguchi,²⁴ questioned Reed's discovery that yellow fever is due to a filtrable virus and reported *Leptospira icteroides* as the cause. This mistake was rectified 10 years later by the work of Sellards³³ and others. Subsequently, outbreaks of yellow fever appeared elsewhere in America, but as they were controlled within a short time, it was still thought possible to stamp out the disease.

In 1920, the Rockefeller Foundation sent to West Africa an expedition headed by General Gorgas. He died in London, but his assistants carried on, and finding evidence of the existence of yellow fever, they recommended further studies. In 1925, General F. F. Russell, who was recently retired as Director of the International Health Board, sent out a second expedition, under Major Henry Beeukes, to work in Nigeria and on the Gold Coast. After 2 years of intensive search for an experimental animal, Stokes, Bauer, and Hudson⁴² (1927) found that monkeys (*Macacus sinicus* and *M. rhesus*) from non-endemic countries were susceptible to infection. This fundamental discovery has made possible many advances in our knowledge of the disease.

Since that time, 32 mosquito species of the genera: *Aedes*, *Culex*, *Mansonia* and *Anopheles*, have been incriminated as yellow fever vectors, and certain flies, bedbugs and ticks have been shown to be mechanical carriers of the virus.⁴¹ In 1929, Sawyer, Lloyd, and Kitchen³⁹ developed a method for the preservation of yellow fever

virus, by drying it in a vacuum while frozen, thus making it possible to transport the virus to research laboratories in America. In 1930, Theiler⁴⁴ showed that white mice are susceptible to intracerebral injections of virus, and this afforded a more convenient experimental animal. The following year, Sawyer and Lloyd²⁹ (1931) developed the so-called mouse "protection test" which is now being used in a world-wide immunity survey. Recovery from an attack of yellow fever is followed by the appearance of virus-neutralizing antibodies, which remain in the serum throughout life. Therefore the "protection test" can be used to determine the periods during which the disease has existed in any community.

The use of this test supplemented by pathologic methods, has recently led to the discovery that in certain countries, where yellow fever has been eliminated from the towns and cities by mosquito control, the disease still exists in sparsely settled jungle regions, in spite of their freedom from *Aedes aegypti*. Soper,⁴⁰ who has studied this jungle type of yellow fever since 1932, reports that although urban outbreaks may decline or cease for a time there is a vast, previously unknown, reservoir of infection in the interior of South America. The endemicity of the disease, instead of being limited to a few scattered areas, as was once thought, extends over large parts of Brazil, Bolivia, Paraguay, Peru, Ecuador, Venezuela and Columbia. Last year, during a survey made of Indians in the San Blas Islands about 50 miles from Colon, members of the Army Medical Research Board, Ancon, C.Z., found an individual less than 10 years old who gave a positive protection test.

Recognition of the existence of jungle yellow fever naturally has caused the Rockefeller Foundation to abandon its original program of world eradication, based on the destruction of *Aedes* in key centers,²⁸ and has introduced many new problems such as: 1, a search for the still unknown vectors and hosts of the jungle infections; 2, methods to protect individuals exposed in endemic regions; and 3, precautions against the spread of the disease from the jungle areas to "*Aedes*-infested" urban centers. Such spread has been traced in a few outbreaks in Brazil and Bolivia. The increasing facilities for rapid transit make it important to guard against more serious accidents.

With this in view the countries concerned have adopted mutually protective agreements and the Pan-American Airways system is taking special precautions to avoid accidental transportation of infected mosquitoes or passengers. These precautions will include: 1, the vaccination of all flying personnel as soon as practicable; 2, careful inspection of passengers to eliminate those infected and, 3, systematic destruction of mosquitoes on all airplanes.

Recent experimental work on yellow fever vaccination indicates that eventually a prophylactic suitable for military use may become available. The vaccine of Theiler and Smith⁴⁶ (1936) which is

prepared with an attenuated strain of tissue-culture virus, protects lower animals and is now being used in man.

For over 30 years the United States Army has enjoyed an armistice with its ancient foe, the Yellow Jack, but we must be prepared for a renewal of hostilities at any time. Yellow fever could easily cause serious damage, should it be introduced into the United States during the summer, or should it become epidemic among troops operating in an endemic region. If we are to protect our forces under field conditions, some effective method of immunization must be made available. It is hoped that this may be accomplished by the "Theiler-Smith" vaccine.

Dengue Fever. Dengue, or break-bone fever, is a non-fatal disease of some military importance. It is endemic in warm climates throughout the world, and often occurs in extensive epidemics. One of the earliest clinical descriptions of the disease was contributed by the distinguished Benjamin Rush, of this university, who was responsible for the medical organization of the Army in 1777. His studies on dengue were made during a severe outbreak which occurred in Philadelphia in the summer of 1780.

The transmission of dengue is, in many ways, similar to that of yellow fever. The work of Graham¹⁶ (1903) in Syria indicated its mosquito transmission, and later studies of Bancroft³ (1906) and of Cleland, Bradley, and McDonald⁹ (1917-1919) incriminated *A. aegypti*. Various members of the Army Board in Manila have added to our knowledge of dengue. In 1907, Colonels Ashburn and Craig² proved that it is caused by a filtrable virus in the blood; and they transmitted it mechanically through *Culex fatigans*.

Colonel J. F. Siler and his associates³⁵ (1925-1928) carried out extensive studies of dengue transmission by *A. aegypti*. Their conclusions have been summarized as follows:

"a. Previous reports of the transmission of dengue fever by *Aedes aegypti* were amply confirmed (47 instances).

"b. *Culex quinquefasciatus* was eliminated as a possible transmitting agent (7 attempts to transmit all of which were negative).

"c. The patient with dengue fever can infect the mosquito in the late incubationary stage of the disease (6 to 18 hours prior to the onset of symptoms, as manifested by elevation of body temperature above normal) and ordinarily continues to be infective to *Aedes* mosquitoes during the first 3 days of illness.

"d. When the mosquito draws blood from an individual during the first 3 days of his illness, under conditions ordinarily encountered in nature, the virus must remain in the mosquito for a somewhat definite period of time before the mosquito is capable of infecting a human being through its bites. Under the conditions existing when the Board carried out its experiments (cool, dry season in the tropics), this time interval was found to be from 11 to 14 days.

"e. After the infected mosquito has become capable of transmitting the virus to human beings it retains that capacity throughout the remainder of its life (experimental dengue in humans was produced with mosquitoes infected 62, 66 and 75 days previously).

"f. The virus causing dengue fever is not carried from the infected mosquito through its eggs to the next succeeding generation.

"g. For all practical purposes the incubation period of dengue fever in human beings may be considered as being from 4 to 6 days, inclusive.

"h. An attack of dengue is followed by a period of increased resistance to the infection (at least for several weeks or months), but the duration of the immunity was found to be exceedingly variable. There was no evidence of racial immunity. The permanent population living in areas of endemicity develops a high degree of immunity, the most logical explanation being that it results from somewhat frequent, repeated, mild attacks."

Schule³² in 1928 observed that *A. aegypti* may become infective as early as the 8th day after ingesting dengue virus, when the atmospheric temperature and humidity are relatively high. Later Army workers (Simmons, St. John and Reynolds³⁸) investigated the disease with the following results:

a. *Aedes albopictus*, a common oriental mosquito, was shown to be an effective biologic vector, the mechanism of transmission being similar to that for *A. aegypti*.

b. Dengue was transmitted mechanically from individuals in the acute stage of the disease to susceptible persons, through interrupted feeding of either *Culex quinquefasciatus* or *A. aegypti* provided large numbers of mosquitoes were used.

c. The virus in the mosquito was shown to be filtrable.

d. Virus was transmitted from infected to normal mosquitoes without passage through a mammalian host.

e. Native Filipinos living in mountainous regions beyond the range of *Aedes* were shown to be susceptible to dengue, while comparable groups of natives in endemic areas were highly immune.

f. It was shown for the first time that dengue could be transmitted through mosquitoes from man to certain species of monkeys caught in non-endemic regions and back to man. Adult monkeys of the same species from endemic areas were found to be immune. This suggested the possibility that a dengue "reservoir" might be maintained in uninhabited jungle areas by passage of the virus through the susceptible young of monkeys or other animals, as has since been shown to be the case in Jungle Yellow Fever.

g. Dengue virus failed to penetrate the excoriated skin of human beings.

h. Experimental observations indicated that dengue produces a somewhat high degree of immunity, certainly for a period of several months to more than a year.

i. A saline suspension of macerated infected *A. ægypti* used as a vaccine failed to confer demonstrable immunity.

In 1931, it was shown by Holt and Kintner¹⁷ that in infected *A. ægypti* the virus is present in all parts of the body.

Much has been added to our knowledge of the virus of dengue and of the epidemiology and transmission of the disease by workers in various parts of the world, including: Cleland, Bradley and McDonald,⁹ Koizumi, Yamaguchi and Tonomura,¹⁹ Manoussakis,²¹ Blanc and Caminopetros,⁴ Blanc, Caminopetros and Manoussakis,⁵ Blanc, Caminopetros, Dumas and Saenz,⁶ Snijders, Dinger and Schüffner.³⁹

The present importance of dengue to the army is due almost entirely to its high incidence among troops in the Philippines. For 37 years a large proportion of the soldiers, stationed in and around Manila, have contracted the disease at some period during their stay. The annual incidence curve has fluctuated at intervals which appear to be correlated with the importation of susceptible troops, and has shown no sustained improvement during this period. As most of the adult native residents of Manila are immune to dengue, and as yellow fever does not exist there, the civil authorities have not regarded complete *Aedes* control as important enough to warrant its cost.

Dengue rarely kills, and is of relatively short duration, however it is a potential military hazard because of its widespread endemicity and its tendency to occur in epidemics which incapacitate large groups of persons within short periods of time. For example, in the summer of 1885, three-fourths of the inhabitants of Austin, Texas, were sick with dengue;³⁴ and in 1897, half the population of Galveston was infected. During the great epidemic of 1922 over a million people were attacked in our southern states; and during 1927-1928 about a million and a half cases occurred in Greece. We can all visualize conditions under which such an epidemic, striking during the critical period of a decisive campaign, might jeopardize the success of our armies. To avoid such an unfortunate occurrence an effective vaccine is needed for the protection of troops in the field.

Malaria. Among all the diseases of mankind, malaria deserves the unsavory title of "Public Enemy No. 1." We who enjoy the present, relative security of our northern cities, are apt to think vaguely of malaria as an interesting, but disagreeable, disease which is visited mainly on the lazy natives of southern climes. The fact of the matter is that these "shiftless natives" belong to a great tropical empire which stretches around the earth, and is peopled by millions who have been conquered and enslaved by malaria.

Sir Patrick Manson concluded that, "malaria causes more deaths, and predisposition to death, than all the parasites affecting mankind together;" and Osler designated malaria as the "greatest single destroyer of the human race." Today, in spite of our accumulated knowledge concerning its etiology, treatment and control, this dis-

ease exceeds all others in sapping the vitality, and impeding the social, industrial, and political progress of the inhabitants of many tropical countries.

The Army's experience with malaria has been largely satisfactory; and our relative success in its control has undoubtedly helped to develop a false sense of security. A century ago malaria caused more than 25% of the disease admissions to Army hospitals, while since the World War the proportion has been only 1%.

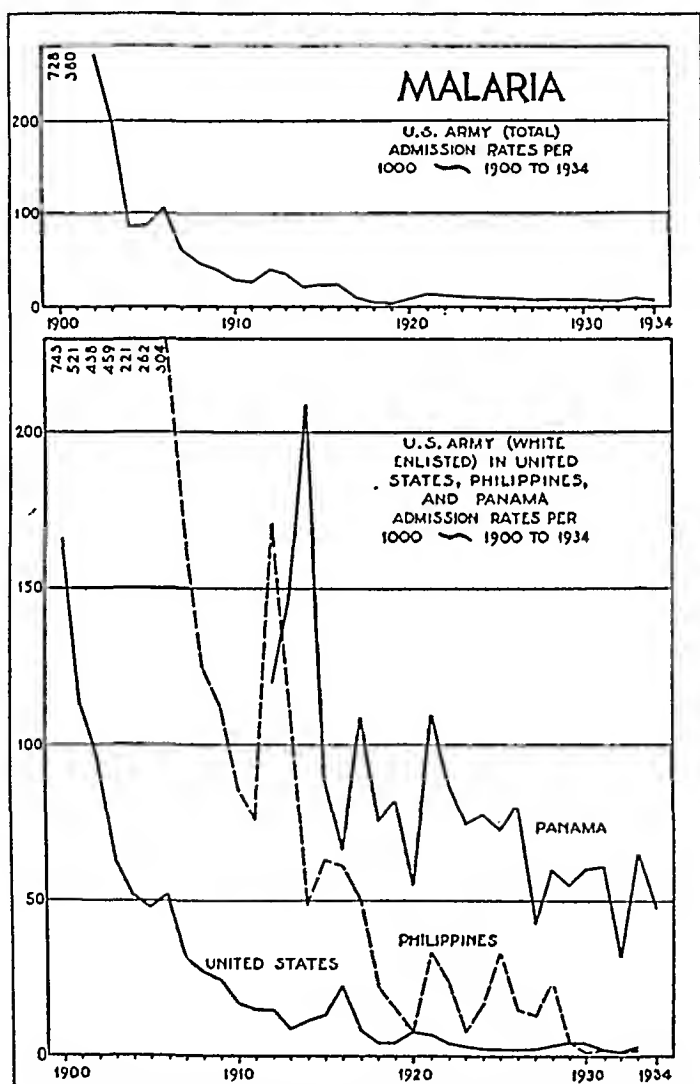


FIG. 1.—From unpublished manuscript, "Malaria in Panama," by Simmons, Callender, Curry, Schwartz and Randall, 1937.

The modern campaign against the disease began after 1898, when the studies of Manson, Ross, Grassi, and others had incriminated certain anopheles mosquitoes as vectors. The results are indicated by the annual admission rates per 1000 among white enlisted men, which are shown in Fig. 1.

As is indicated by the upper curve, the malaria admission rates for the total Army declined from 728 per 1000, in 1900, to 380 the next year; and since 1916 they have been almost negligible.⁷ The incidence curve for troops in the Continental United States was the first to fall, the rates being about 165 per 1000 in 1900, 50 in 1907, and less than 10 since 1920.

Conditions were quite different in our Philippine stations, and during the early days a large proportion of our troops there contracted malaria. The rates decreased gradually from a high of 743 per 1000 in 1900, to less than 50 in 1918, and since 1930 they have been negligible. The present low incidence affords spectacular proof of the value of the experimental studies of Colonel C. F. Craig¹⁰ and others, and to the effective field work of many Army sanitarians.

The experience of our troops in the Panama Canal Zone has been less satisfactory. The trend of the malaria incidence curve has been downward, but even as late as 1933 the rate was 65.9, which was 20 times the rate among troops in the United States, and 34 times the rate for our white soldiers in the Philippines.⁴³ This comparatively high incidence of malaria among the soldiers in Panama may be due in part to differences in the mosquito vectors of the regions concerned. In the Philippines, the important vector is *Anopheles minimus*, a mosquito which breeds in rapid, foot-hill streams, above sea level. In Panama, the chief carrier is *A. albimanus* and there are several other effective vectors, some of which prefer to breed in sunlit, still waters, others in well shaded jungle streams, and still others in tidal swamps, thus rendering their control more difficult and costly. Before 1934 only 4 of the 15 recognized anophelines of the Canal Zone were known to be malaria vectors, and since that time, Rozeboom²⁷ of the Gorgas Memorial laboratory has incriminated *A. bachmanni* and Simmons³⁶ of the Army Board has incriminated 4 additional species, including *A. punctimacula*.

Since the early days of the Spanish Conquistadores, the Isthmus of Panama has been notorious for its pestilential fevers, especially yellow fever and malaria. Both of these plagues, but mainly malaria, contributed to the failure of DeLesseps' attempt to build the French canal, during which at least 20,000 lives were lost and more than 260 million dollars were spent.

In 1904, when Gorgas began his well-known sanitary campaign¹⁵ which made possible the construction of the present canal, he was armed with the knowledge that malaria is transmitted by anopheline mosquitoes. Also he had practically unlimited funds to use for mosquito control. As shown in Fig. 2, the malaria rates among canal employees decreased from a high of 821 per 1000 in 1906 to a low of 16 in 1916.⁷ By continuing the anti-mosquito work at a present cost of about \$130,000 annually, this decrease in malaria has been maintained, but there has been no progressive improve-

ment during the last 20 years. As shown in Fig. 2, the malaria rates among troops are much higher than those for canal employees.

The persistence of malaria in the Canal Zone, in spite of the vigorous measures taken to prevent it, indicates the difficulty of mosquito control in the American tropics. The relatively large annual appropriations have been sufficient only to eliminate the

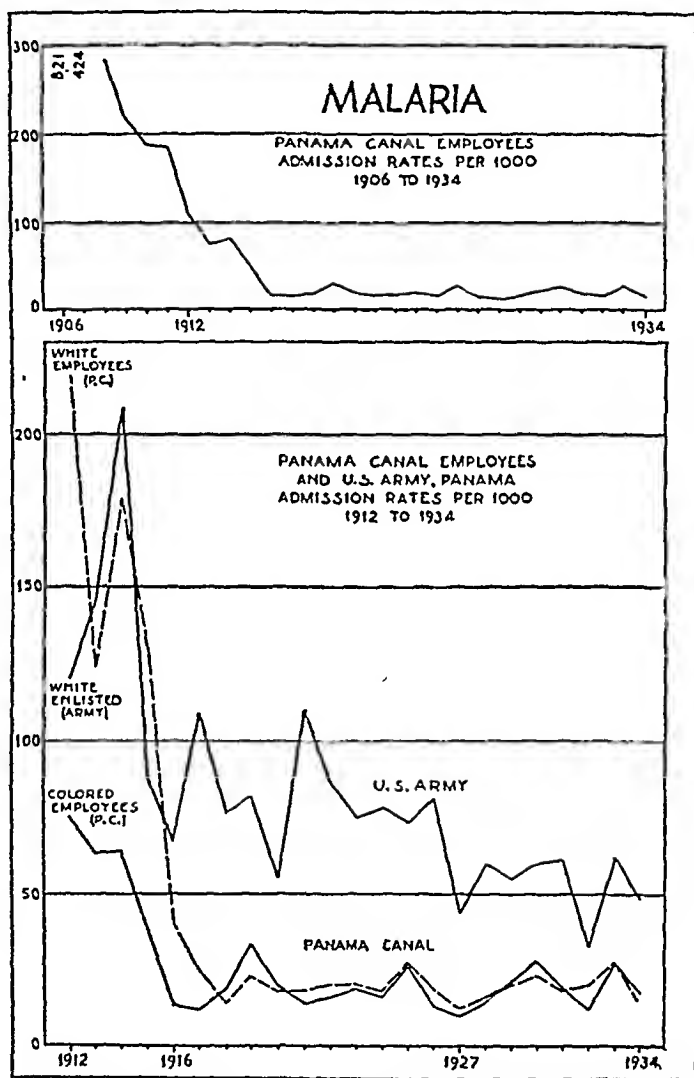


FIG. 2.—From unpublished manuscript, "Malaria in Panama," by Simmons, Callender, Curry, Schwartz and Randall, 1937.

mosquito breeding in small areas, which extend for 1 to 3 miles around the cities of Colon and Panama, the Canal Zone towns and the permanent military posts. (Chamberlain)⁷. These areas are surrounded by a great unsanitated region including the rest of the Zone and the Republic of Panama, in which mosquitoes continue to breed unhindered. From these vast breeding places, many anophelines

invade the sanitated areas each year, coming either in nuptial flights or in search of blood (Curry¹²).

Malaria is highly endemic among the natives living in and around the Zone, and the incidence of human carriers is high (Clark and

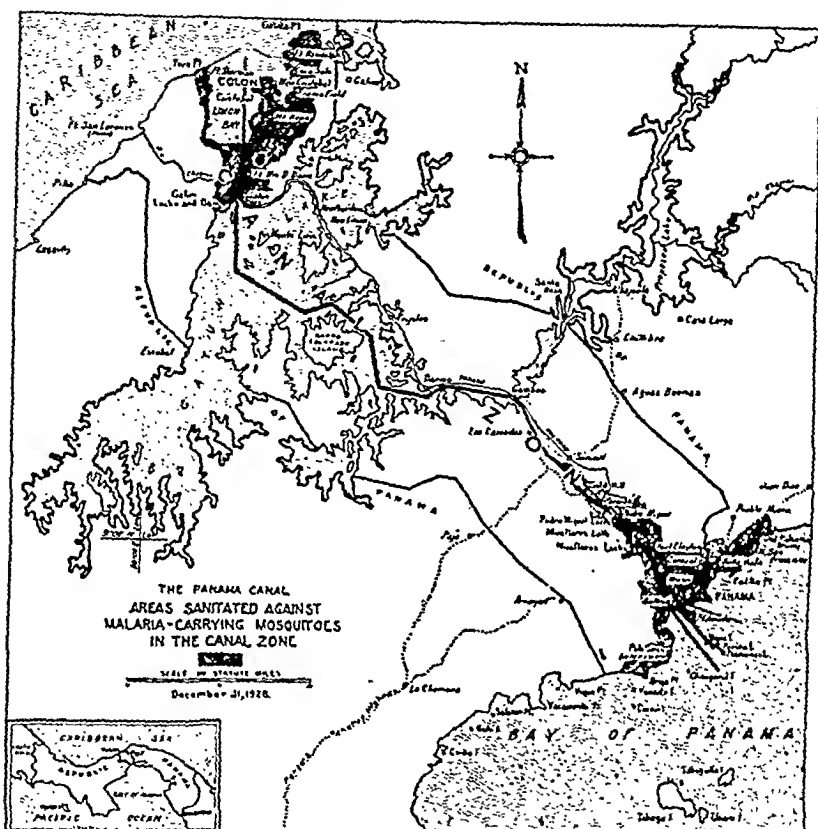


FIG. 3.—The channel of the Canal is represented by the heavy black line from Cristobal and Limon Bay on the Caribbean side to Balboa and Panama Bay on the Pacific side. The two lighter lines, at a distance of 5 miles on either side of the Canal, are the boundaries between the Canal Zone and the Republic of Panama. The Canal Zone also includes all of Gatun Lake, together with a narrow border of land around it, and the basin of the proposed lake in the upper Chagres River basin. The total area sanitated against malaria is shown in heavy shading about the two terminals of the Canal. Within these sanitated areas are concentrated the bulk of the Canal employees, as well as the military forces and their families. Elsewhere in the Canal Zone practically all employees and their families are furnished thoroughly screened quarters, but no antimosquito work is carried out. Farmers, known as "Zone settlers," live outside the sanitated areas and are unprotected against malaria. (From the official records of the Health Department of the Panama Canal.)

Komp⁸). Therefore the invading mosquitoes have many opportunities to become infected before their arrival. Surveys made by the Army Board during the past 2 years show that a significant proportion of the *Anopheles* caught in barracks are infected.

The greater prevalence of malarial fevers among the troops,

compared with Canal employees, is probably due to various factors, including the following: 1, the soldiers may be more susceptible as they are young, white adults who remain in Panama only 2 or 3 years, while over 50% of the employees have lived there for 10 or more years, and may have developed some resistance to the infection; 2, most of the Army posts are located nearer the unsanitized jungles than are the Canal Zone towns; and are nearer mosquito breeding areas; 3, the soldiers are exposed to mosquitoes, not only in the sanitized areas, but also while on reconnaissance trips and maneuvers in unsanitized regions.

During such periods of exposure, special precautions are taken to prevent malaria.⁴³ The men are required to sleep under mosquito nets, and are warned against visiting native villages after dark. They are also given quinine in daily doses of 15 grains. The latter procedure is of distinct military value, but only because it delays the development of clinical symptoms while it is continued. As quinine does not kill sporozoites, it fails to prevent infection, and therefore it is not uncommon for many men to develop the clinical symptoms of malaria after they return to barracks and discontinue the drug. Obviously, an effective field prophylactic is urgently needed and for several years atabrine and other therapeutic agents have been tried experimentally, but so far with inconclusive results.

The great prevalence of malaria in Panama is well illustrated by an incident which occurred during maneuvers held recently near the Canal Zone border. As these maneuvers took place during the "dry season," it was decided to omit the use of quinine prophylaxis. Before the end of the second week, so many cases of malaria had developed that the continuation of the exercises was seriously interfered with.

Such occurrences show the importance of malaria as a military problem, and indicate the need for the development of more effective methods for the prevention of this disease in the field. The difficulties encountered by troops living under the relatively favorable peace time conditions which exist in the Canal Zone, afford a serious warning of the dangerous situation that would undoubtedly arise should it become necessary for our army to operate for a long period in the American tropics.

Equine Encephalomyelitis. Another mosquito-borne disease of some interest to our Army is equine encephalomyelitis. This is an epizootic disease which occurs sporadically in various parts of the United States, and is caused by a filtrable virus, which may be identical with the virus of Born disease. In 1933, Lieut. Col. Kelser,¹⁸ at the Army Medical School, transmitted the virus to horses through *Aedes aegypti*, and since that time several other species of *Aedes* have been incriminated as potential vectors (Simmons, Reynolds and Cornell;³⁷ Merrill, Lacaille and Ten Broeck;²³ Madsen and Knowlton²⁰). The disease has not been common among army

animals but obviously it might occur at an inconvenient time and interfere with military movements.

The work of Kelser, moreover, is of considerable importance to human medicine as this was the first demonstration of the transmission of a purely neurotropic virus by mosquitoes. This fact naturally reopens the question as to whether certain acute infections of the central nervous system in man may also be carried by insects, and suggests many problems which still require investigation.

Conclusion. In this review, an attempt has been made to outline, briefly, the progress made in the Army's fight against some of the diseases caused by mosquitoes; also to point out certain weaknesses in the present lines of defense. The investigations of a host of civilian and military workers have armed us with information concerning the etiology of these diseases, and under favorable conditions we are able to prevent them by the tedious and costly method of eliminating their insect vectors.

Unfortunately, such methods of control cannot be applied effectively by an army actively engaged in the field, and we are still unable to protect adequately, troops operating in regions where these diseases are prevalent. To afford this protection, we must have effective, specific prophylactic agents, either drugs or vaccines. The search for such agents should be an important part of our Nation's preparedness program. This problem concerns not only the Medical Corps, but the whole medical profession, and it is hoped that eventually their combined efforts may lead to new victories in our War in the Air.

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A STATISTICAL STUDY OF ACUTE HEMORRHAGIC PANCREATITIS (HEMORRHAGIC NECROSIS OF PANCREAS).

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THE belief that alcohol is in some way related to acute hemorrhagic pancreatitis has developed in this department from a review of the clinical story in fatal examples of this disease. This has been fortified by a not infrequent case with an explosive clinical course and striking postmortem findings. The following abstracts will illustrate:

Case Abstracts. CASE 1.—A healthy American girl of 16, with no previous relevant history, in the course of an evening drank two moderately large glasses of Italian wine. Intoxication followed shortly thereafter but no other symptoms or signs were present. Shortly after going to bed at midnight, she vomited and experienced severe pain across the abdomen and back. The symptoms persisted until 4 A.M. when she is said to have fallen asleep. At 7 A.M. she was found dead.

Autopsy (No. 1685) disclosed numerous petechiæ in the gastric mucosa and an extraordinary pancreas. The duodenum, gall bladder and bile ducts showed no apparent lesions. The ampulla of Vater was patent. The pancreas was large, boggy and both externally and on cut section, revealed large, confluent dark red and purple-black patches between which

were still seen thin yellow-pink streaks of normal parenchyma. The tail of the pancreas was most involved and the head least. No abnormality of the pancreatic ducts was discovered. Microscopically, diffuse hemorrhage disrupted the tissue everywhere; the latter was necrotic—only the shadowy outline of cells remained. A few areas of intense leukocytic infiltration and fat necrosis were found, but by and large, cellular reaction was absent.

CASE 2.—A 30-year-old white male had both hands blown off in an explosion a year before his death. Physical recovery left him unhappy and he embarked upon a course of progressive alcoholism, so that shortly before his death he was consuming a quart of wine or whisky daily. On the day prior to admission he drank 2 quarts of sherry. Not long thereafter he began to vomit violently and experienced severe abdominal pain, especially in the epigastrium. The violence of the symptoms showed no abatement and he was sent to the hospital on the following day. On admission, he was critically ill and writhing in agony. There was a strong odor of alcohol on his breath. The abdomen was rigid and diffusely tender, most marked in the right upper quadrant. Immediate laparotomy revealed a hemorrhagic pancreatitis, with fat necrosis and peritonitis. A cholecystostomy was performed. The patient died less than 24 hours after admission.

Autopsy (No. 3873) showed a fatty liver, fibrino-purulent peritonitis and a pancreas similar in appearance to that described in Case 1. The body and tail were diffusely dark red. Microscopically, hemorrhage and necrosis predominated, although fat necrosis and leukocytic infiltration were occasionally prominent. In a few zones, proliferating young connective tissue suggested earlier insults of a similar type. No duct abnormalities were demonstrated.

In the light of such findings an analysis of the 4000 autopsies in our series was undertaken. Each anatomic diagnosis was reviewed and all protocols in any way related to pancreatic disease were abstracted, with especial emphasis on the clinical history (including alcoholism), the chief anatomic causes of death and also the post-mortem condition of the stomach, pancreas, liver and gall bladder. All the available slides of liver and pancreas in these cases were reviewed. These cases were subdivided as defined below.

Acute Pancreatitis. All cases of hemorrhagic necrosis or acute pancreatitis not relevant to the present analysis were excluded. Those excluded were:

1. Associated with septicemia or systemic infection (scarlet fever, typhoid fever, tuberculosis, etc.).
2. Due to direct extension from a neighboring infection (peritonitis, retroperitoneal abscess, etc.).
3. Unequivocally related to severe passive congestion (usually associated with heart failure.).
4. Associated with widespread hemorrhagic tendency (purpura, leukemia, etc.).
5. Associated with carcinoma of the pancreas or neighboring structures.
6. The result of direct trauma to the pancreas (*e. g.*, bullet wound).

These lesions varied from pure hemorrhage to simple leukocytic invasion, and from tiny focal to extensive diffuse processes.

All instances not easily placed in the above categories were listed (Table 1). Of these, there were 38, or 0.95% of 4000 autopsies.

In 25, or 66% of the 38, alcohol was a probable factor. Only 6, or 15.8%, also has disease of the gall bladder. Although the duct systems were not examined with equal care in all instances, it is interesting that grossly observable obstruction to the pancreatic ducts was found only twice (Nos. 735 and 1117). In one (735) a stone at the ampulla of Vater produced a common channel between the common bile duct and pancreatic duct. In the other (1117), although a gall stone was present at the ampulla, there was some question in the mind of the operator whether a functioning common channel could have existed. No significant age distribution was noted. Thirty cases (79%) occurred in males. The pancreatic damage was often diffuse and the direct cause of death; often focal and apparently incidental to the cause of death. A direct but rough correlation existed between the time of death and the degree of inflammatory reaction; practically all of the instances with pure hemorrhage and necrosis occurred in patients who lived but a few hours. Several showed chronic inflammatory reaction or fibrosis in the pancreas. There was no demonstrable correlation between the amount of alcohol consumed and the degree of pancreatic involvement. In many of the protocols the stomach was noted to contain food. No. 2596 may be considered vascular in origin, but because of the prominence of the necrosis it was included in this series. The inclusion of No. 3577 may also be questioned. The patient was known to have long-standing hypertension and increasingly severe attacks of angina pectoris. During the course of an injection of 95% alcohol into the thoracic sympathetic ganglia he died rather suddenly after receiving a total of 6 cc. At autopsy, some acute congestion of the viscera was found, but nowhere, hemorrhage comparable to that in the pancreas.

Alcoholism. As a check on the high percentage of cases found associated with ingestion of alcohol, the attempt was made to ascertain the incidence of pancreatic disease in alcoholism. This was done in three ways.

1. *Acute Alcoholism.* The incidence of pancreatic lesions was studied in the group of patients who died during acute alcoholic episodes. The manner of death seemed unimportant, providing a reliable history, or more significantly, postmortem analysis indicated the presence of alcohol. In 4000 autopsies 51 such cases were found. Of these, 27, or about 53%, showed pancreatic lesions; 25 were acute and 2 chronic reactions.

In the course of reviewing these 51 cases the impression was gained but could not be substantiated that the rate of postmortem autolysis in the pancreas was considerably accelerated in instances of acute alcoholism.

2. *Chronic Alcoholism.* In 4000 autopsies there were 41 instances of chronic alcoholism. None of these at the time of death were under the influence of alcohol. Nineteen, or about 47%, showed pancreatic lesions, almost all of a chronic nature.

TABLE 1.—ACUTE HEMORRHAGIC NECROSIS OF PANCREAS (ACUTE PANCREATITIS).

Aut. No.	Age.	Sex.	Pancreas.					Alcohol.	Biliary tract.	Metaplasia.	Other comment.
			Necr.	Item.	Fat necr.	Ac. in-flam.	Fibro.	Foc. or diff.			
735	83	F	+	+	2+	Diff.	2+	Stono lodged in amp. of Vater with common channel. Acute cholangitis.
1057	60	M	=	=	...	Diff.	Diabetic coma.
1117	68	F	4+	4+	4+	2+	...	Diff.	Stono in common duct with ? obstr. in amp. of Vater. Chr. cholangitis. Common channel.
1149	40	F	3+	2+	3+	4+	2+	Diff.	"Prolonged alcoholic debauch recently"	...	Death followed much alcohol consumption.
1501	51	M	+	+	Many focal Diff. mainly body and tail	Death several hrs. after acute onset with vomiting.
1085	10	F	4+	4+	+	+	...	Diff.;	"2 large glasses of Italian wine; intoxication"	...	Moderate portal cirrhosis of liver. Failed for drunkenness, dead in morning. "Undigested food in stomach."
1772	45	M	+	=	+	...	#	Focal Diff.	Found dead.
1884	30	M	4+	4+	Diff.	"Intoxicated"	...	Found dead. Small pieces of food in stomach.
2025	53	F	2+	+	3+	+	+	Diff.	Found dead.
2034	68	M	3+	3+	Focal Diff.	"Wino in stomach"	...	Found dead.
2126	35	M	2+	4+	Diff.	Found dead.
2278	60	M	4+	4+	Diff.	"Drinking for 2 to 3 days"	...	Died suddenly. Much undigested food in stomach.
2380	55	M	74+	3+	Diff.	"Drinking for 2 days"	...	Marked portal cirrhosis of liver.
2450	70	F	=	+	+	=	2+	Diff.	Chronic alcoholic	2+	"Alcoholic intoxication." Dead 15 mins. after arrival hosp.
2469	40	M	=	4+	Diff.	"Odor of alcohol in stomach and viscera"	...	Much undigested food in stomach.
2581	33	M	+	2+	Diff. in body and tail	Found dead.

2596	40	M	2+	4+	Diff. in tail and body	Syphilitic mesoarteritis.
2896	52	M	?	=	Multiple focal	Found dead. Stomach contained many food particles.
2920	45	M	?3+	3+	Focal	Found dead. Stomach filled with food. Fractured cervical vertebra from fall.
2922	27	M	4+	2+	+	Diff.	Much semisolid food in stomach.
2967	64	M	=	3+	Focal	Portal cirrhosis of liver.
3007	50	M	=	+	Diff.	"Food debris in stomach."
3008	45	F	?4+	+	Diff.	Found dead. Much semisolid food in stomach.
3021	64	M	4+	2+	3+	Diff.; mainly head	Found dead.
3027	25	M	?2+	=	Multiple focal	"Much recently ingested food in stomach."
3068	36	M	?4+	+	Diff.	Much food in stomach.
3088	54	M	?4+	=	Diff.	Many food particles in stomach.
3097	67	M	?4+	2+	Diff.	Semisolid food in stomach.
3184	40	M	2+	...	3+	Diff.	Pancreatic duct dilated but not obstructed.
3229	69	M	?2+	=	Focal	Found dead.
3290	45	M	?4+	=	Diff.	Found dead
3304	43	M	...	+	Multiple focal	Found dead
3308	45	M	4+	4+	Diff.	Stomach "distended with partially digested food." Found dead.
3577	63	M	=	4+	Diff.	Died suddenly 25 min. after beginning of alcohol inject. in thoracic ganglia for angina pectoris.
3812	43	F	4+	4+	4+	Diff.	Chr. and acute cholecystitis with stones	...	Fatty liver. Found dead.
3817	50	M	?3+	+	Multiple focal	+	Skull fracture with extradural clot. Found dead. Vomiting for several days.
3820	69	M	...	=	Focal	Cholelithiasis	...	Pain and vomiting—onset after drinking 2 qts. sherry.
3873	30	M	4+	4+	4+	2+	...	Diff.	"Heavy drinker of alcohol"	...	

3. *Cirrhosis of Liver.* In 4000 autopsies there occurred 51 instances of periportal cirrhosis of the liver. All examples of cirrhosis which were clearly biliary, toxic (*e. g.*, carbon tetrachloride), cardiac or associated with hemochromatosis were excluded. Of the 51 cases of the periportal variety, 25 (49%) showed pancreatic lesions. These also were practically all of a chronic nature.

The incidence of acute pancreatitis in the 4000 autopsies is about 1% (38 cases) and of chronic pancreatitis (or fibrosis of the pancreas) about 2.5% (97 cases). These results indicate an increase of 40 to 50 times in the incidence of pancreatic disease in the alcoholism group.

Further Relationships. No statistical analysis of hemorrhagic pancreatitis would be adequate without studying its relationship to the biliary tract. For despite many discrepancies, all observers are agreed in maintaining that hemorrhagic pancreatitis is associated in a high percentage with disease of the biliary tract. Figures vary considerably but reach as high as 60%.⁵

By the term "extrahepatic-biliary tract disease" is indicated not only acute or chronic inflammatory lesions, recognized grossly or microscopically, but also gall stones, with or without associated inflammatory change. Excluded are uncomplicated neoplasms. In the 4000 autopsies including all ages, there were 343 instances (8.6%) of extrahepatic-biliary tract disease. These figures are in agreement with most autopsy series, which find the incidence to be about 10% of all adults.

In the present series, extrahepatic biliary tract disease was found 6 times in the group of acute pancreatitis and 21 times in the chronic pancreatitis group,* an incidence of 15.8 and 21.7%, respectively.

This is a significant rise in incidence as compared to the 8.6% in the 4000 autopsies. It agrees in substance if not in degree with other published data.

The other aspect of this problem, namely, the incidence of pancreatic lesions in biliary tract disease, has usually been neglected. The 6 cases of acute pancreatitis and the 21 cases of chronic pancreatitis were distributed through 343 cases of biliary tract disease, giving an incidence, respectively, of 1.8 and 6.1%. This is but slightly greater than their occurrence in the general autopsy series (1 and 2.4%, respectively).

The various writers who have stressed the frequent association of biliary tract disease with hemorrhagic pancreatitis have looked upon the former as primary, although they have been at a loss to explain the mechanism. In a small proportion of cases—less than 10%—the so-called "common channel" theory of Opie⁹ has been

* All fibroses—interacinar, interlobular or focal—as well as chronic inflammatory reaction of the pancreas in adults are included in this term. This excludes the large number of chronic pancreatic lesions in congenital syphilis.

referred to. In this series of 38, as already mentioned, only 1 and possibly 2 cases—at most 5.3%—are thus explainable. In contrast, the following 3 cases are presented with a “common channel” but no pancreatitis.

CASE 3.—A 53-year-old negress with known hypertension died in the hospital with symptoms of cerebral involvement.

At autopsy (No. 1125) generalized arteriosclerosis with cerebral thrombosis and rheumatic heart disease with congestive failure explained her death. In addition, a thick-walled gall bladder filled with stones was found. We quote from the protocol. “It is thought advisable to open both the duct of Wirsung and the common bile duct from above downward. The duct of Wirsung . . . and the common bile duct . . . both open into a common ampulla. The common duct is not increased in size. It is filled with a green viscid bile. In this terminal dilatation (ampulla of Vater) just before it narrows into the orifice of the ampulla, a stone (5-sided, soft and pearly-white in color) is found jammed. It can be expressed through the opening in the common duct when pressed upon. It is the only stone found in the bile ducts.” The pancreas was normal grossly and microscopically.

CASE 4.—A 48-year-old white female, because of frequent gall bladder colic, submitted to a cholecystectomy. The pathologic diagnosis was chronic cholecystitis with cholelithiasis. Following a short period of T-tube drainage of the common duct, convalescence progressed smoothly and bile appeared in her stools. During the next few months, however, several attacks of colic were experienced. Following the last attack she became jaundiced, had several chills and died shortly after admission to the hospital.

At autopsy (No. 2622) there was found an encapsulated accumulation of bile in the gall bladder bed with a fistulous communication to the common and hepatic ducts, a severe cholangitis with liver abscesses, and a stone wedged firmly into the ampulla of Vater. The main pancreatic duct opened into the ampulla; the duct itself was neither stained nor otherwise remarkable. The common bile duct was thickened and dilated. A large accessory duct was found in the pancreas which opened separately into the duodenum 3 cm. distal to the ampulla. The pancreas was grossly normal; microscopically, there was an infiltration of neutrophils in the connective tissue of the head only.

CASE 5.—A 63-year-old white male with several attacks of gall bladder colic finally submitted to an operation. The gall bladder was distended. A cholecystoduodenostomy was performed but the patient died several days later.

At autopsy (No. 1842) there was found a chronic and acute cholecystitis and cholelithiasis, dilatation of the common, hepatic and pancreatic ducts which opened into a common ampulla and rupture of the anastomosis between the gall bladder and duodenum, with peritonitis. No stone was found at the ampulla of Vater, although it was dilated to 1.5 cm. in diameter. The pancreas was grossly negative and microscopically showed a few perivascular lymphocytes.

Another factor recently brought into the limelight¹² in the pathogenesis of acute pancreatitis has been the metaplasia of the pancreatic duct epithelium. The general occurrence and anatomic features have been described in detail by Priesel¹¹ and Baló and Ballon.³ Rich¹² has directed attention to duct obstruction in the

causation of acute pancreatitis and has ascribed to these metaplastic nodules the rôle of obstructing agent in a high percentage of these cases.

In the course of the present review, attention was especially directed toward the state of the duct epithelium. The slides of 261 pancreases were examined. These included 84 normal pancreases, 63 with some form of acute reaction and 114 with fibrosis or chronic reaction. Included among these chronic forms were instances of congenital syphilis. A total of 32 cases with metaplasia of the duct epithelium were found. Three of these occurred in the group of acute pancreatitis (Table 1), 5 were in normal pancreases and 24 in pancreases showing fibrosis or chronic pancreatitis.

Comment. The rôle of alcohol in the causation of acute pancreatitis is by no means clear. Only sporadic cases are sufficiently dramatic to attract attention to the alcohol. The majority show pancreatic involvement of an essentially minor nature—and are therefore easily overlooked. In addition, the wide use of alcohol probably has contributed to the neglect of its rôle as a causative factor.

Isolated reports have appeared from time to time in the literature. For instance, in 1907 Egdahl⁶ analyzed 105 cases of acute pancreatitis. His largest number (42%) was associated with gall bladder disease; the next in infrequency consisted of 32 cases following gastro-duodenitis, of which 17 were associated with alcohol. In 1934, Myers and Keefer⁸ analyzed 29 cases of pancreatic necrosis, 22 of chronic pancreatitis and 24 of focal fat necrosis and, respectively, found 12, 7 and 9 associated with either cirrhosis of the liver, fatty liver or acute and chronic alcoholism, that is approximately one-third. Isolated case reports have also been published. That of Adams and Bouloux¹ is representative. They recorded a boy aged 20 who collapsed after drinking rum and died in 20 minutes. At autopsy, the sole pathologic lesion was fresh hemorrhage in the pancreas. Several others drinking the same rum were unaffected.

How does alcohol act? Egdahl⁶ assumed that it was merely the cause of the gastro-duodenitis which in turn caused the pancreatitis. Myers and Keefer⁸ discussed several theories: 1, that alcohol in the blood damages the pancreas directly; 2, that duodenal congestion obstructs or infects the ducts; 3, that persistent vomiting causes regurgitation of duodenal contents into the ducts. Rich¹², on the basis of Gizelt's work,⁷ believed that alcohol like food stimulated pancreatic secretion and that the pancreatitis resulted from rupture of acini whose excretory ducts were blocked by metaplastic epithelium.

No theory of the pathogenesis of acute pancreatitis is offered in this communication. Attention, however, is directed to a few facts. The presence or absence, the severity or rate of progress of the pan-

creatic lesion does not appear to vary with the quantity of alcohol ingested.

Apparently, it may attack an individual who has had little or no previous indulgence (Case 1), while it may completely spare a chronic and severe alcoholic. Alcohol alone is not enough.

Several other sets of data, detailed above, deserve comment.

The high incidence of biliary disease with pancreatitis is accepted by many and yet without presenting the reverse of this relationship, most writers have assumed that biliary disease causes pancreatitis. It is desirable therefore again to repeat what the data included in this communication show: *that the incidence of gall bladder disease is significantly increased in pancreatitis but the incidence of pancreatitis in gall bladder disease is only slightly (if at all) higher than in the general autopsy series.* This is doubly interesting because in recent years several investigators^{4,10,14} have been revising the interpretation of the "common channel" concept. The finding of pancreatic enzymes in the gall bladder has led them to postulate a pancreatic reflux, and a few^{4,14} have ascribed to this mechanism an important rôle in the causation of cholecystitis. Popper,¹⁰ who does not believe the evidence for such causation sufficient, has published, however, a series of figures which bear mention. He removed bile sterily at operation in 219 instances—210 direct from the gall bladder and 9 from the choledochus. In 37 (17%) he demonstrated the presence of pancreatic ferments; several were from bacteriologically and microscopically normal gall bladders. In 18 cases of acute hemorrhagic pancreatitis in which he examined the bile, ferments were found in 16 (88%).

The simplest interpretation of Popper's results is that in acute pancreatitis there is an obstruction to the outflow of pancreatic secretion, which takes the path of least resistance, when a "common channel" is present. This explanation assumes that obstruction is all-important in the pathogenesis of this disease; and, as Rich¹² has shown, the rupture of the acini with escape of the enzymes into the surrounding tissue initiates the pathologic processes. Other experimental work¹³ is also in agreement with this. The instances in which the classical mechanism first described by Opie⁹ operates, may be explained similarly, *i. e.*, by obstruction to the outflow of pancreatic secretion. All experimenters who have produced pancreatitis experimentally by the injection of bile into the pancreatic ducts, have injected the material under pressure, or else used infected bile. Archibald² injected sterile bile into the pancreatic ducts of cats and was able to produce only a relatively transient edema. Cases 3, 4 and 5 which are abstracted above, show at least that a stone impacted in the ampulla of Vater with a resultant "common channel" is not necessarily followed by pancreatitis.

The mechanism of obstruction to the pancreatic ducts is by no

means clear. In a few instances an impacted stone at the ampulla, a tumor or other extrinsic masses pressing on the pancreatic duct may be operative. In our own series, anatomic obstruction was not found more than a few times, although dilated pancreatic ducts were not infrequent, especially in a few cases of chronic pancreatitis. Archibald's² explanation of either edema of the papilla of Vater or a spasm of the sphincter of Oddi, although based on animal experimentation has never been proved in human cases.

In what percentage of acute pancreatitis obstruction is operative, and what other factors are involved must for the present remain unanswered. No one can fail to be impressed by the complexity and multiplicity of factors involved in this disease.

Summary. 1. A review of 4000 necropsies at the New Haven Hospital revealed 38 (1%) with acute hemorrhagic pancreatitis and 97 (2.4%) with chronic pancreatitis.

2. In 25 (66%) of the acute cases, alcohol was an associated factor. In 6 (15.8%) disease of the extrahepatic biliary tract was present.

3. In 51 instances of individuals dying during acute alcoholic episodes, 27 (53%) showed pancreatic lesions (25 acute and 2 chronic).

4. In 41 instances of chronic alcoholism, 19 (47%) showed pancreatic lesions, all of a chronic nature.

5. In 51 instances of periportal cirrhosis, 25 (49%) had pancreatic lesions.

6. In 343 cases of extrahepatic biliary tract disease, there were 6 instances of acute pancreatitis and 21 of chronic pancreatitis, an incidence of 1.8 and 6.1%, respectively.

7. The present material shows that the incidence of gall bladder disease is significantly increased in pancreatitis; but the incidence of pancreatitis in gall bladder disease is only slightly (if at all) higher than in the general autopsy series. While the data offer no relation to the pathogenesis of acute pancreatitis, they indicate at least the complexity of the problem.

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THE NATURE AND THE MECHANISM OF STAINING OF THE ERYTHROCYTIC RETICULUM.

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It is generally accepted, especially since the exhaustive experiments of Key,¹ that the reticulum of young erythrocytes is not a preëxisting structure, but the pattern formed by the action of the vital stains on the basophilic substance of the "polychromatophilie" cell, while the cell is still wet. This pattern and the site it occupies within the cell varies with the different dyes; however, in its general appearance it is always characteristic of the particular stain. Because brilliant cresyl blue acts more uniformly and much faster than any of the others, it is now the most common vital stain used for the demonstration of the reticulum in the routine laboratory technique. Inasmuch as the colors of the brilliant cresyl blue and of the methylene blue are indistinguishable, one might believe that the reticulum continues to retain the color of the brilliant cresyl blue stain after counterstaining. Invariably, however, specimens stained with the brilliant cresyl blue alone and kept either uncovered or mounted with Canada balsam, lose their stain within a short time, while the counterstained specimens usually preserve the stained reticulum almost indefinitely. Still, at times, a few counterstained preparations, when examined at a later date, are found to be void of the reticulum or show the same in a faded state without any apparent staining disturbance of the basophilic structure of the white blood cells, while other preparations, made simultaneously and at times mounted on the same slide, continue to show the reticulum brilliantly stained. To explain the cause of this discrepancy, and at the same time to investigate further the nature of the basophilic substance, especially as to its staining mechanisms, is the purpose of this paper.

Blood specimens from patients with pernicious anemia in induced and spontaneous remission, sickle-cell anemia and anemia of hemorrhage, showing a reticulocyte count of over 20%, were used. After gentle defibrination, small amounts of cells were placed in centrifuge tubes and stained by mixing with an almost equal amount of solutions of various stains in 0.85% of sodium chloride. After it had been established, by proper wet and dry preparations, that the reticulum was well stained, the dye was removed by repeated washings with 0.85% solution of sodium chloride. After the last centrifugation the excess sodium chloride solution was discarded and wet and dry preparations were examined to ascertain that the cells showed no trace of the stain, *i. e.*, no trace of a demonstrable reticu-

lum. Films from such specimens were then stained with the Wright's stain in the usual manner. It was then observed that the cells showed a reticulum brilliantly stained blue, in a percentage corresponding to the known reticulocyte percentage of the fresh specimen. The reticulum always appeared blue, regardless of the color of the vital dye originally used (*e. g.*, neutral red) and without any demonstrable difference from a fresh specimen in pattern or brilliance. The pattern remained characteristic of the vital stain used and corresponded to the known pattern for that particular stain.

Similar experiments were then carried out on slides. Blood films, stained with vital stains of different colors, such as brilliant cresyl blue and neutral red, were fixed with methyl alcohol and then flooded with water. This process removed all trace of the vital stain. After drying, the slides were stained with Wright's stain in the usual manner. The reticulum reappeared on these slides always brilliantly blue, regardless of the color of the vital stain, and always assumed the characteristic pattern of the particular dye.

These results were more simply, but even more clearly, illustrated when, in place of counterstaining with the Wright's stain, another vital dye of a different color than the first was used. The vitally stained blood films were fixed with methyl alcohol, flooded with water sufficiently to remove the vital stain, and dried in the air. A drop of a solution of a vital stain of a different color than the one used at first was then placed on a cover slip, and this inverted and deposited over the slide. The reticulum then reappeared showing the pattern of the first stain but in the color of the second. If, for example, brilliant cresyl blue was first used and then neutral red, the reticulum appeared red but in the characteristic pattern of the brilliant cresyl blue. If the stains were used in the reverse order, the reticulum appeared blue but had the neutral red pattern.

Discussion. These experiments seem further to confirm the theory that the reticulum-forming material is a structureless, protoplasmic substance, evenly distributed in the stroma of the young erythrocyte, decreasing as the cell matures. Methyl alcohol, or similar fixative agents, causes a uniform precipitation of this substance, which takes basic stains. The uniform bluish staining of the stroma of such cells presupposes such a condition. The intensity of staining depends upon the amount of the basophilic substance present. The introduction of the so-called vital stain in the wet preparation causes a flaky precipitate. The shape and size of these flakes, as well as their arrangement within the cell, differ with the different vital stains used. These flakes, the "reticulum," are not permanently stained with the vital stain (the brilliant cresyl blue, for instance, in the routine blood technique) but such stain is dissolved and washed off during the process of counterstaining. Then the reticulum is restained with the methylene blue of the counter-

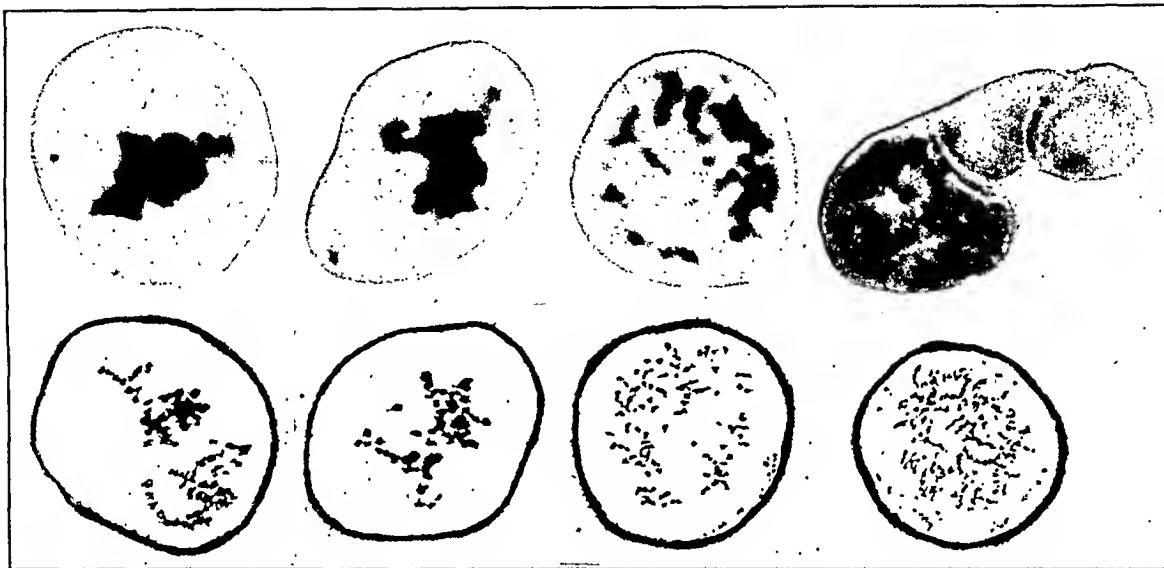


FIG. 1.—Forms of reticulum in red blood cells. The upper row shows photographs and the lower row camera lucida drawings of red blood cells stained as follows: (1) Neutral red. (2) Neutral red, washed, then Wright's stain. The red color is replaced by blue. (3) Methylene blue. (4) Brilliant cresyl blue. The amount of reticulum substance is greater in the more immature cells than in the older forms, and the sparse granules of the older forms are much the same with any of the stains. With brilliant cresyl blue the fine granules tend to form filaments. With methylene blue the filaments are finer and shorter. With neutral red the granules are coarser, and clumping is common.

staining material, more, as it seems, permanently. The permanency of such staining then seems to depend upon the more or less complete removal of the brilliant cresyl blue. When small amounts of the counterstaining material are used, and then the preparation is not flooded with water for the purpose of differentiation, but, instead, only a few drops of water are used, apparently most or some of the brilliant cresyl blue is retained which later fades out, causing the reticulum to "disappear." If such preparations are then restained with the Wright's stain, the reticulum reappears as bright and as brilliant as is shown on the fresh preparations. For this reason, it seems that, during the counterstaining process, an excess of stain and an excess of water, as much as the slide or cover slip will hold, should be used to make sure that the brilliant cresyl blue is redissolved and completely replaced by the more stable methylene blue.

Summary. 1. Reticulum in immature erythrocytes is a precipitate caused by the interaction between a basophilic substance in the cell and the vital dye.

2. In counterstaining the reticulocytes with Wright's stain, the reticulum stain is replaced by methylene blue.

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ACUTE HEMOLYTIC ANEMIA.

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Two cases of acute hemolytic anemia of the Lederer⁹ type form the basis of this report. The first closely resembles the other 55 cases thus far reported; the second is unusual in that autoagglutination of the patient's blood was observed. As far as I know, this phenomenon, rare in itself, has been seen only twice before in cases of acute hemolytic anemia (Giordano and Blum⁵; Patterson and Smith¹⁴).

Case Abstracts. CASE 1.—E. T., a female aged 6, was first seen on January 23, 1934, because of vomiting, fever and jaundice. On January 19 the child felt chilly, had an elevation of temperature to 101° F., and complained of headache. Vomiting began the following day and was persistent and profuse. The mother also noticed at this time that the child was jaundiced and that the urine looked bloody. The symptoms were more pronounced when I saw the patient on January 23. At this time there was intense jaundice, severe pallor, restlessness, and dehydration. The spleen and liver could not be felt. The urine looked bloody, but did not have the coffee-ground appearance that it has in hemorrhagic nephritis;

subsequent examinations of the urine showed no red cells but the presence of large amounts of hemoglobin. A diagnosis of acute hemolytic anemia was made and hospitalization advised.

The child was admitted to this hospital on the same day and was immediately given 300 cc. of Type I blood by direct transfusion from the father. A few hours after the transfusion definite improvement was seen. Examination of the blood before transfusion showed the following: Many reticulocytes, anisocytosis and poikilocytosis; red blood cells, 800,000; white blood cells, 12,900 with 85% neutrophils, 13% lymphocytes, and 2% eosinophils; and platelets, 300,000. The hemoglobin was 20% (Sahli). Fragility of the red cells was normal; hemolysis began at 0.425 and was complete at 0.250. The test for fragility was repeated later and found to be essentially the same, 0.425 to 0.275. The Donath-Landsteiner test was negative. Blood cultures taken on the 23d and 25th of January were negative. The blood contained 114 mg. % sugar, 61 mg. % urea, 1.8 mg. % creatinine, 138 mg. % cholesterol, 11.3 mg. % calcium, 3.02 mg. % inorganic phosphorus, and 1.05 mg. % bilirubin. The total non-protein nitrogen was high, 111 mg. %. The indirect Van den Bergh reaction was ++. The urine contained hemoglobin and large amounts of albumin. The temperature remained elevated (101° to 102.2° F.) for 2 days and then subsided. For other blood examinations see Chart 1.

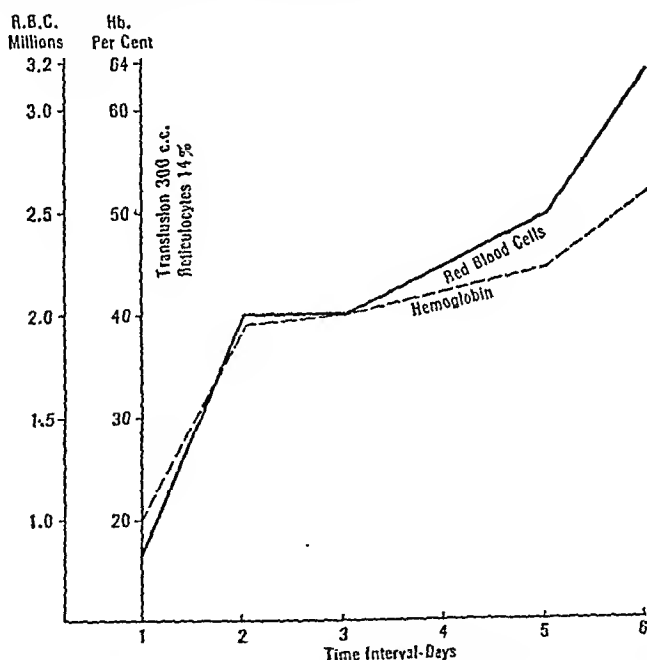


CHART 1.—Case 1. Hemoglobin content and red blood count before and after transfusion.

The anisocytosis and the poikilocytosis persisted for several days; the reticulocytes disappeared within 48 hours after the transfusion. The child was discharged 6 days after admission to the hospital.

CASE 2.—J. H., a female aged 5, was first seen on December 24, 1936, because of headache, jaundice, pallor, and bloody urine. The parents stated that the child had a sudden rise in temperature to 103° F. 3 days before and at the same time vomited and complained of severe abdominal

pain. The following day severe pallor and jaundice were observed; at this time, too, the urine was bloody. The family physician said that intense restlessness had been present from the beginning and had been uninfluenced by large doses of phenobarbital.

Physical examination revealed an acutely sick child with extreme pallor and frank jaundice; the mucous membranes of the mouth were dry. The sensorium was cloudy. The liver and spleen could not be palpated. A loud systolic murmur was heard at the third intercostal space at the left sternal border. The temperature was 104° F. A diagnosis of acute hemolytic anemia was made and hospitalization was advised.

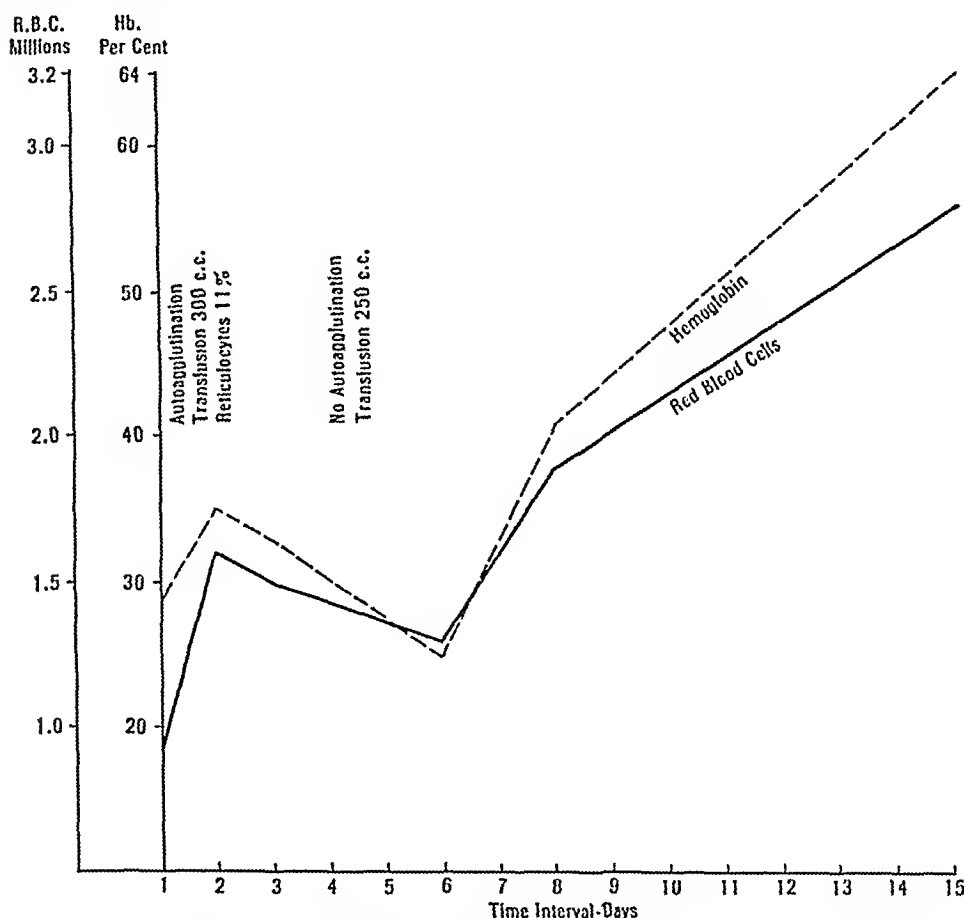


CHART 2.—Case 2. Hemoglobin content and red blood count before and after transfusion.

On admission to the hospital arrangements for an immediate transfusion were made. Delay was encountered because of the presence of autoagglutination of the patient's blood. The patient's blood clumped when placed on a slide, without the addition of typing sera as well as with the addition of typing sera; thus it was impossible to type the child's blood. The child's condition was becoming more grave and in desperation we decided to use the father, who fortunately was a universal donor. Three hundred centimeters of blood were given slowly by the indirect method, with no reaction. Five days later the autoagglutination was no longer present and it was determined that the child's blood belonged to Group 2. Subsequent examinations of the blood failed to show autohemagglutination. Immediate improvement followed the transfusion; the color improved, the somnolence

disappeared, the vomiting stopped and the child no longer complained of abdominal pain. The temperature ranged from 101° to 102° F. for 4 days and then subsided. On the fourth day of the child's stay in the hospital the spleen could be felt one-half finger's breadth below the costal margin.

Examination of the blood on admission before transfusion showed 890,000 red blood cells, 13,800 white blood cells and 29% hemoglobin content (Sahli); many reticulocytes, poikilocytosis and anisocytosis, and a marked shift to the left in the white cells were observed. The fragility test was normal (0.475 to 0.350). The urine contained 3+ albumin, a large amount of hemoglobin, a considerable amount of urobilin but no red cells. The chemistry of the blood was as follows: sugar, 146 mg. %; cholesterol, 240 mg. %; urea nitrogen, 16.8 mg. %; uric acid, 3.8 mg. %; creatinine, 1.4 mg. %. In this case no non-protein nitrogen retention could be demonstrated; subsequent examinations of the blood also failed to show any retention. The icteric index was 21.5 units and the indirect Van den Bergh reaction was positive. Cultures of the blood were consistently negative. On the fifth day after admission, because of the slow improvement in the blood, another transfusion of 250 cc. of whole blood from the father was given; this was followed by rapid improvement (Chart 2).

There was a gradual decrease in the icteric index and on January 6 the indirect Van den Bergh reaction was no longer positive.

On December 25, 2 days after the first transfusion, a hematocrit study showed a normocytic hyperchromic anemia: red blood cells, 1,600,000; hemoglobin, 6 gm. per 100 cc. of blood; color index, 1.09; volume index, 1.06; saturation index, 1; mean corpuscular volume, 87; mean corpuscular hemoglobin, 37.4 micromicrograms, and the mean hemoglobin concentration, 44%. Chart 2 shows the changes in some of the blood elements following the first and second transfusions.

The child was discharged from the hospital as well on January 8, 1937. Subsequent examinations did not show any abnormal physical or hematologic findings.

Discussion. Acute hemolytic anemia, with or without hemoglobinuria, may result from a variety of infections, poisons (fava bean), or drugs (sulphanilamide). Thus Bartonella infection is an example of a blood infection which produces an acute severe hemolytic anemia with or without hemoglobinuria; here the red cells are invaded by the organisms and broken up. The acute hemolytic anemia of Lederer is a disease of unknown etiology and is characterized by a sudden onset with elevation of temperature, severe anemia, icterus, leukocytosis and, at times, hemoglobinuria.

The age incidence varies from 5 months to 35 years. Parsons and Hawksley¹³ reported 6 cases under 2 years of age and Lederer,⁹ 2 under 2 years. In infants, the clinical course is more rapid, the anemia develops with greater speed and is more severe than in adults.

The Clinical Picture. The onset is sudden and occurs with fever which may range from 99° to 105° F.; diarrhea, vomiting, abdominal pain, severe headache, and marked restlessness are outstanding symptoms. In 24 to 48 hours and sometimes longer, weakness, marked pallor, and definite jaundice develop. The liver and spleen sometimes become enlarged at this stage. From observations on my cases and from a study of the cases reported, it is my impression

that there are two distinct phases in the symptomatology of this disease. In the first phase, which lasts from 24 to 72 hours or longer, the symptoms resemble closely those seen in any severe infectious disease; from the appearance of the patient and even from careful hematologic studies it is impossible even to suspect that a serious blood crisis is impending. In the second phase, the hematologic crisis dominates the picture; *i. e.*, the marked pallor, the severe jaundice, the rapid and sharp drop in the red cells and in hemoglobin content of the blood completely obscure the previous train of symptoms. Thus, in 3 cases observed from the beginning of the disease it was noticed that a drop in red cells from 4,500,000 to 600,000 to 800,000 occurred within a few hours. As a rule, the temperature lasts from 4 to 5 days.

The restlessness observed early in the disease is not due to air hunger since it is present when the hemoglobin content and red cell count are still fairly high. Later the restlessness is due, without doubt, to the anoxemia which results from the severe anemia. Hemoglobinuria was seen only once in 9 cases by Parsons and Hawksley,¹³ twice in 6 cases by Lederer,⁹ once in 1 case by Patterson and Smith,¹⁴ twice in 2 cases by Giordano and Blum,⁵ and twice in 2 cases by the author. It seems that hemoglobinuria is encountered in the severe cases and probably results from the sudden hemolysis of a large number of red cells. Hemic murmurs are frequently noted and are usually systolic in time. In 1 case, however, diastolic murmurs at the base have been described.¹¹ These murmurs, whether systolic or diastolic, disappear on recovery from the anemia; my second patient had a loud systolic murmur which subsequently disappeared. It is the consensus of opinion that these murmurs are temporary and more or less harmless. It is believed by some, however, that Moseheowitz's¹² case is an instance of this disease in which organic cardiac changes were found. Mosehcowitz reported the case of a patient who had a severe hemolytic anemia which proved to be fatal. Necropsy showed hypertrophy of the left ventricle of the heart; microscopically, every field revealed from 1 to 12 thrombi in the terminal arterioles or capillaries. Careful study of his case, however, shows no resemblance to the disease described in this communication except for the severe anemia. For example, his case showed a marked increase in the fragility of the red cells, petechiæ, and hemiparesis, manifestations not observed by any other author. Retinal hemorrhages have been reported by Holst⁶ and by Lederer⁹ and are more characteristic of the disease in adults than in children. Blood cultures have been negative in the cases thus far reported.

Hematology. The red cell count varies from 600,000 to 1,500,000 to 2,000,000 and the hemoglobin content from 10 to 40%; anisocytosis and polychromasia are always present; occasionally, poikilocytosis is also observed. The color index is about unity or above;

reticulocytes and erythroblasts are found in large numbers; macrocytes, basophilic stippling and megaloblasts are also seen—all evidence of a vigorous attempt on the part of the bone marrow to repair the anemia.

The fragility of the red cells, the bleeding and coagulation time, and the platelet count are normal. When hemolysis is rapid and severe, an increase in the number of white cells with many young cells is found. The number of white cells may be as low as 3000¹⁵ or as high as 80,000;^{5,9} thus it is evident that the disease can be confused with leukemia.

Generally, the blood picture is that of a hyperchromic megalocytic anemia; this, together with the marked increase in reticulocytes, is characteristic of a profound anemia with hyperfunction of the bone marrow. The second case described in this communication, however, showed a normocytic hyperchromic anemia; the myeloblasts, too, were not as numerous as in some of the cases reported by other observers.

The indirect Van den Bergh is positive, the icteric index is high (20 to 90 units) and urobilinogen is found in the urine. As a rule, there is a marked non-protein nitrogen retention; it was present in 1 of the cases reported here; the urea nitrogen was 61 mg. % in 1 case but only 16.8 mg. % in the other. In 1 case reported by Lederer⁹ the urea nitrogen ranged from 59 to 98. In all cases normal values are found after recovery is well established. Whether this increase is due to a temporary renal insufficiency, as Lederer believed, or whether it is due to the accumulation of protein products resulting from the marked increase in blood destruction it is difficult to say. Because of the rapid return of these values to normal after transfusion it is logical to believe that the latter view is the correct one.

Etiology. No definite etiologic factor has been found thus far, and all attempts to determine the cause of this disease have been unsuccessful. The sudden onset with fever suggests that the disease results from some infection, but thus far no definite infectious process has been demonstrated; this was true in the 2 cases observed by the author. Repeated blood cultures were negative and repeated physical examinations failed to show any evidence of infection. Witts,¹⁸ however, states that the disease may be ushered in with sore throat and influenzoid symptoms. It is possible and even likely that no single etiologic factor is responsible for the disease.

Lederer believed that the exciting factor, probably infectious in nature, acts as an irritating stimulus on the reticulo-endothelial system with consequent increase in the blood destruction.

From a study of the course of this disease and its hematologic picture, it seems that there are two possibilities for consideration as far as pathogenesis is concerned; first, that there is produced in this disease during its primary phase some hemolytic agent which

rapidly breaks up a large number of red cells and that the large number of myeloblasts, erythroblasts and reticulocytes found in the blood results from a strong effort on the part of the bone-marrow to make good the sudden deficiency; and, second, that the cells are rendered more fragile and break up rapidly even in the absence of any new hemolyzing agent because some toxic substance is produced which acts on the bone marrow to prevent the production of normal and properly functioning erythrons. The author believes that the first view is the correct one for the following reasons:

1. The bone marrow apparently is able to respond to the tremendous demands made upon it, as judged by the large number of reticulocytes and erythroblasts in the blood: 67% reticulocytes have been reported in 1 case by Fiessinger, Decourt and Lour⁴ and 43% in another by Patterson and Smith.¹⁴

2. Recovery is complete and takes place in a comparatively short time in every typical case; this is not true of other blood dyscrasias in which the bone marrow is at fault.

3. In no disease in which the bone marrow is depressed or disturbed in its function does the dramatic response follow transfusion as it does in acute hemolytic anemia; only a true substitution therapy will produce an effect comparable to this one. Thus, it is the author's belief that, when a transfusion is given, antihemolytic agents are introduced in sufficient numbers to prevent further excessive hemolysis.

The rôle of hemautoagglutination in the etiology of this disease is not clear. Hemautoagglutination is a clumping of erythrocytes into irregular masses visible to the naked eye and occurring in the presence of the individual's own serum at room temperature and reversible at body temperature.

In autoagglutination there is a definite interaction of agglutinin in the serum with the agglutigen in the red cells; however, the union can occur only at a temperature below that of the body. It is important, therefore, in collecting blood for examination, that the vessel be warm and kept warm by placing it in a water bath at 39° C.; when typing smears, warm slides should be used. Had these precautions been taken in Case 2 we would have had no difficulty in matching the child's blood. Only about 25 true cases of autoagglutination have been thus far reported. This phenomenon has been observed in pernicious anemia and other severe anemias, in acholuric jaundice with marked enlargement of the spleen, in a case of multiple myelomas with hyperproteinemia, and paroxysmal hemoglobinuria, in severe pneumonias and in staphylococcus septicemia.^{1,7,16,17} It has been observed in only 3 cases of acute hemolytic anemia. The first case was reported by Patterson and Smith¹⁴ in 1936, the second by Giordano and Blum⁵ in 1937, the third case is reported in this communication. The autoagglutination persisted for 21 days in Giordano and Blum's case, for several weeks

in Patterson and Smith's case, and for 5 days in the author's case. It is doubtful whether this phenomenon is responsible for the acute hemolytic process in this disease; it is more likely that the auto-agglutination is a phenomenon which appears during the height of the disease as it does in other severe anemias, and disappears on recovery. It is even problematic if it ever enhances hemolysis; for example, it was present for 21 days in Giordano and Blum's case, yet improvement after one transfusion was striking and continued. No apprehension need be felt as to any ill effects from transfusion provided the blood of the patient and that of the donor are properly matched and cross-matched. It is advisable, however, to use the indirect method, to make sure that the donor's blood is kept at body temperature; it is also suggested that the patient be placed under some heating apparatus. It is unnecessary and at times even undesirable to begin the transfusion with extremely small amounts of blood. None of the 3 patients showed any ill effects from the transfusions although fairly large amounts of blood were injected; three transfusions of 300 to 500 cc. each were given. Giordano and Blum's patient had a mild immediate reaction but his temperature dropped and the general condition improved within a short time.

Differential Diagnosis. In children, the disease may be confused with acute leukemia and with acholuric jaundice, particularly if the patient is seen during a crisis. The confusion with leukemia occurs because of the vigorous response of the bone marrow to the sudden increased hemolysis, with the result that large numbers of immature white as well as red cells are sent out into the circulation. When the total count is high, as it is in some cases, the mistake is even more likely to occur. The therapeutic test, however, should unequivocally determine the diagnosis. In acute hemolytic anemia, the response to transfusion is dramatic, whereas in leukemia the patient is certainly not benefited and, at times, his condition is even aggravated by the procedure. The differential diagnosis from acholuric jaundice is at times extremely difficult because in both conditions fever, severe abdominal pain and intense jaundice may be present at the onset. There is a considerable number of cases of acholuric jaundice which go unrecognized until a crisis occurs. The outstanding differentiating characteristics are the family history, the increased fragility, the microcytosis, the absence of hemoglobinuria, and the enlarged spleen in acholuric jaundice. Large numbers of reticulocytes are found in both diseases. The spleen may be enlarged in acute hemolytic anemia, but the increase in size is rarely present before the third or fourth day of the disease; moreover, the spleen never attains the size observed in acholuric jaundice. The differentiation may become very difficult if the microcytosis and the increased fragility are absent in acholuric jaundice, as occurs in 10 to 15% of the cases.² It is suggested that, if acholuric jaundice

is suspected and microcytosis and increased fragility are absent, other members of the family be examined for these changes. The differentiation between acholuric jaundice and acute hemolytic anemia is of more than academic significance, particularly in the light of the results shown by Doan in his recent work in acholuric jaundice. Doan and his co-workers³ advise splenectomy during a crisis and have reported excellent results with this procedure. Transfusion, while it acts as a specific in acute hemolytic anemia, is of little benefit and perhaps even harmful when given during a crisis to a patient suffering from acholuric jaundice. Obviously, splenectomy, performed on a patient suffering from acute hemolytic anemia of the Lederer type, would be calamitous.

The prognosis is good provided the diagnosis is made early; recovery rapidly ensues upon the institution of proper treatment which consists of transfusion. Usually one transfusion is sufficient, although occasionally more than one may be necessary. The response to transfusion is remarkable and appears to act as a specific. A transfusion should be given as soon as the diagnosis is made, or even if the disease is suspected. It miraculously changes in a few hours the clinical picture of an alarmingly ill patient who seems about to die to that of one on the road to recovery.

How the transfusion acts is a moot question. It is believed by some that the beneficial effect may be due to the fact that some deficiency factor is supplied, thus aiding in the production of normal red cells.⁵ It is more likely, however, that the transfusion achieves its remarkable results, first, by supplying an antilytic agent; this is undoubtedly its most important effect; second, by sparing a very much overworked bone marrow and not by stimulating it as Kuhl,⁸ Manfredini,¹⁰ and Giordano and Blum⁶ believe. As evidence of this there is the marked reduction in the number of reticulocytes which practically always follows a single transfusion. In Patterson and Smith's¹⁴ case the number of reticulocytes was 43% before transfusion; after transfusion there was a gradual decline to 2%; third, by relieving the anoxemia and by tiding the patient over a critical period.

Summary. 1. Two cases of acute hemolytic anemia of the Lederer type are described; in 1 case the unusual phenomenon of hemautoagglutination was observed.

2. Clinically, there are two phases in this disease. The first phase is characterized by fever, vomiting, abdominal pain, somnolence and restlessness; there is nothing to distinguish the disease in this stage from the initial stage of any other severe infectious disease. The second phase is characterized by a sudden severe hemolytic crisis which results in frank jaundice and in a severe anemia of the hyperchromic megalocytic type.

3. The hemaautoagglutination is not responsible for the hemolysis but may interfere with the proper examination and typing of the blood unless special precautions are taken.

4. It is suggested that the disease is due to the introduction or evolution of some hemolytic substance which rapidly destroys large numbers of red cells; the opinion is also advanced that the bone marrow is neither depressed nor primarily at fault but that, on the contrary, the bone marrow makes a vigorous effort to correct the sudden anemia; this is evidenced by the large numbers of reticulocytes, nucleated red cells, and young white cells seen in the blood.

5. Most characteristic is the immediate improvement which follows one transfusion; the theory is advanced that some antilytic agent is introduced with the transfused blood and is responsible for the complete arrest of the hemolytic process.

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OBSERVATIONS ON THE ETIOLOGY OF THE TOXEMIAS OF PREGNANCY.

V. THE ETIOLOGIC RELATIONSHIP BETWEEN WATER RETENTION AND ARTERIAL HYPERTENSION.*†

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In the preceding papers of this series^{3a-f} it has been demonstrated that, in the absence of severe anemia, heart disease and acute nephritis, water retention in pregnancy is conditioned primarily by the level of the plasma proteins, and may be altered, just as in non-pregnant individuals, by changing the intake of electrolytes. It

* Aided in part by a grant from the William W. Wellington Memorial Research Fund of the Harvard Medical School.

† Presented before a joint meeting of the Obstetrical Society of Boston, the New York-Obstetrical Society, the Obstetrical Society of Philadelphia, and the Washington Gynecological Society on April 8, 1938, at Boston, Mass.

has also been shown that, coincident with the induction of marked water retention by the administration of sodium salts in pregnant women with hypoproteinemia, the arterial blood pressure rises and symptoms of preëclampsia may appear.^{3c,d} The observations recorded in this paper indicate that the arterial blood pressure falls and symptoms of preëclampsia disappear coincident with the loss of retained water induced by decreasing the amount of sodium in the diet^{3f} of pregnant women with hypoproteinemia and hypertension arising during pregnancy. These observations therefore represent the converse of those previously reported,^{3c,d} and furnish further evidence that the arterial hypertension encountered in true "toxemia of pregnancy" results from undue water retention conditioned by hypoproteinemia. It must, of course, be recognized that other factors than changes in the sodium intake, such as the intake of other electrolytes, the amount of carbohydrate and nitrogen ingested, as well as the water intake itself, may all influence water balance, particularly in the presence of low plasma proteins.

Arterial hypertension observed in the last trimester of pregnancy will be found in the majority of cases, if the data are available, to have been present before pregnancy, and will also be found to persist after the puerperium. In a small number of cases arterial hypertension appears for the first time during pregnancy as a result of the development in pregnancy of acute glomerulonephritis, pyelonephritis, or benign or malignant nephrosclerosis. It is apparent that these conditions should be designated by their proper names. Difficulty in differential diagnosis does not justify the inclusion of these conditions under the term "toxemia of pregnancy." If this misnomer is to be retained—and only long usage can warrant its retention—it should be applied only to the syndrome characterized by the *initial* appearance of arterial hypertension in the last trimester of pregnancy, and its disappearance after the puerperium in women who do not have glomerulonephritis, pyelonephritis, or nephrosclerosis. This syndrome, often referred to as preëclampsia, is of relatively common occurrence.

Methods. Twenty women in the last trimester of pregnancy with arterial hypertension were selected for study. These women comprised two groups, one composed of 10 women known to have had arterial hypertension prior to pregnancy and exhibiting a similar condition after the puerperium, and a second of 10 women who had normal blood pressures prior to, early in, and after pregnancy.

Upon admission to the hospital all the patients were placed upon house diets without restrictions of any sort. They were not put to bed. Salt and water were allowed freely, but no sodium bicarbonate or saline cathartics were permitted. The arterial blood pressures were determined each morning after the patient had been at rest in a chair for at least 20 minutes. On the morning of the third day or later, the patients were placed on a diet consisting of only 1500 cc. of skim milk daily. Water was allowed freely. The rationale of this procedure and its effect upon weight and water retention have been discussed previously.^{3f}

Observations. 1. The 10 women with known preëxisting arterial hypertension included 7 with essential hypertension, 1 with polycystic kidneys, 1 with probable chronic pyelonephritis, and 1 with probable chronic glomerulonephritis. Their calculated plasma protein osmotic pressure⁴ varied from 217 to 267 mm. of water. They lost from 1.4 to 6.3% of body weight during the 5-day régime of skim milk. In no instance was there a significant change in blood pressure during this period, although hospitalization alone in the preliminary control period was frequently associated with marked declines in blood pressure, particularly in the systolic. Figures 1 and 2 are characteristic records. All the data are summarized in Table 1. In each instance, examination 6 weeks or more post-partum revealed persistent arterial hypertension.

TABLE 1.—THE EFFECT UPON WEIGHT AND BLOOD PRESSURE OF A DIET OF ONLY SKIM MILK IN 10 PREGNANT WOMEN WITH ARTERIAL HYPERTENSION PRIOR TO AND DURING PREGNANCY.

Case No.	Weight loss, %.	Blood pressure change.*		Average "initial" blood pressure.*		Average "final" blood pressure.*		Calculated plasma protein osmotic pressure, mm. H ₂ O.
		Syst.	Diast.	Syst.	Diast.	Syst.	Diast.	
41 . . .	1.4	-13	-8	155	105	142	97	267
42 . . .	1.6	-2	+5	145	92	143	97	262
43† . . .	2.5	+2	-5	146	106	148	101	247
44‡ . . .	2.5	-22	-9	173	112	151	103	225
45§ . . .	3.3	-6	+2	157	94	151	96	237
46 . . .	3.6	-5	-1	146	94	141	93	218
47 . . .	3.7	-5	-1	140	97	135	96	255
48 . . .	3.8	-7	+6	147	80	140	86	232
49 . . .	5.5	-2	0	140	96	138	96	217
50 . . .	6.3	-9	+3	188	100	179	103	220
Average	3.4	-7	-1	154	98	147	97	238

* The "initial" average blood pressure is the arithmetic average of the blood pressures taken on the 3 days preëeding the milk régime, the "final" average is the arithmetic average of the 3 days after the régime, and the change is the difference between these two averages.

† Polycystic kidneys.

‡ Chronic nephritis, probably glomerular.

§ Chronic nephritis, probably pyelonephritis.

It thus appears that the limitation of sodium intake by means of a milk diet resulted in moderate weight losses, but was without significant effect on the arterial blood pressure in 10 women with arterial hypertension in the last trimester of pregnancy who were known to have had hypertension before the pregnancy.

2. The plasma protein osmotic pressures of the 10 women with "toxemia" of pregnancy, as defined above, varied from 172 to 233 mm. of water. These women lost from 3.8 to 8.2% of body weight and became free of visible edema during the period when they received no other food than skim milk. Their arterial blood pressure fell significantly (Table 2). Figures 3 to 7 are characteristic.

Albuminuria decreased in the 9 women who had measurable amounts of albumin in the urine. Five of these 10 women had, besides edema, such preëclamptic symptoms as headache, vertigo, drowsiness, visual disturbances or epigastric pain. Coincident with the loss of weight these symptoms disappeared.

TABLE 2.—THE EFFECT UPON WEIGHT AND BLOOD PRESSURE OF A DIET OF ONLY SKIM MILK IN 10 WOMEN WITH TRUE "TOXEMIA" OF PREGNANCY.

Case No.	Weight loss, %.	Blood pressure change.*		Average "initial" blood pressure.*		Average "final" blood pressure.*		Calculated plasma protein osmotic pressure, mm. H ₂ O
		Syst.	Diast.	Syst.	Diast.	Syst.	Diast.	
51 . . .	3.8	-34	-26	157	110	123	84	218
52 . . .	4.0	-45	-27	163	100	118	73	233
53 . . .	4.5	-31	-21	161	98	130	77	222
54 . . .	4.8	-32	-17	150	100	118	83	225
55 . . .	5.3	-24	-14	151	97	127	83	200
56 . . .	5.5	-41	-22	153	112	112	90	222
57 . . .	6.0	-27	-12	140	92	113	80	185
58 . . .	6.6	-59	-37	189	120	130	83	188
59 . . .	7.0	-32	-33	160	116	128	83	172
60 . . .	8.2	-40	-38	170	128	130	90	175
Average	5.6	-36	-24	159	107	123	83	204

* The "initial" average blood pressure is the arithmetic average of the blood pressures taken on the 3 days preceding the milk régime, the "final" average is the arithmetic average of the 3 days after the régime and the change is the difference between these two averages.

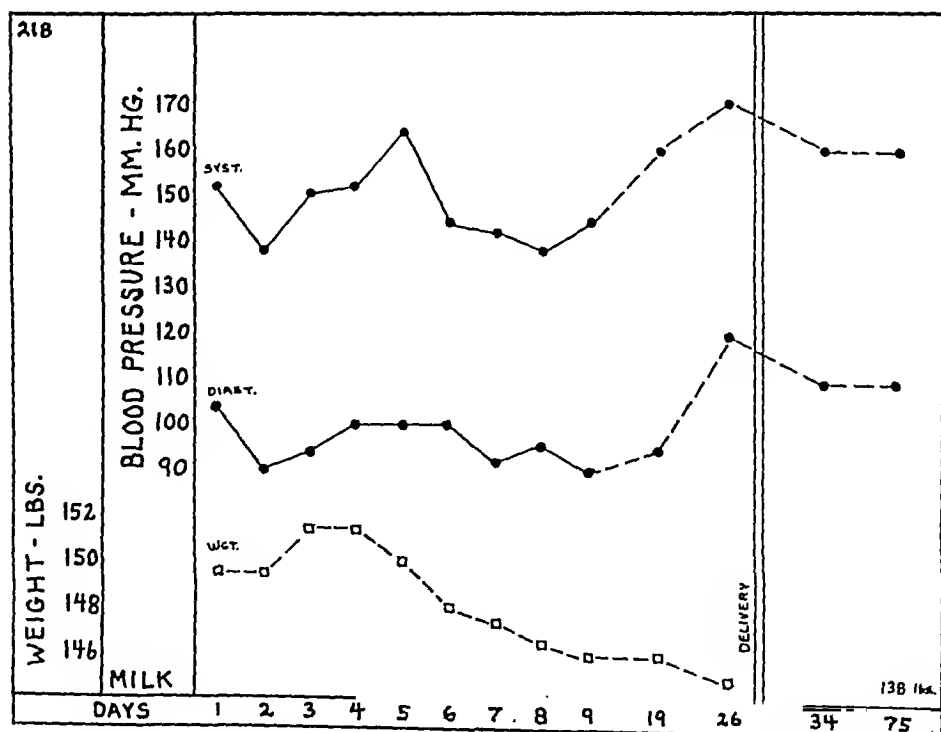


FIG. 1.—Lack of effect of milk diet on blood pressure in case (46) of essential hypertension. Note the rise in pressure in the last week of gestation in spite of continued freedom from water retention and that the blood pressure postpartum was as high as during pregnancy.

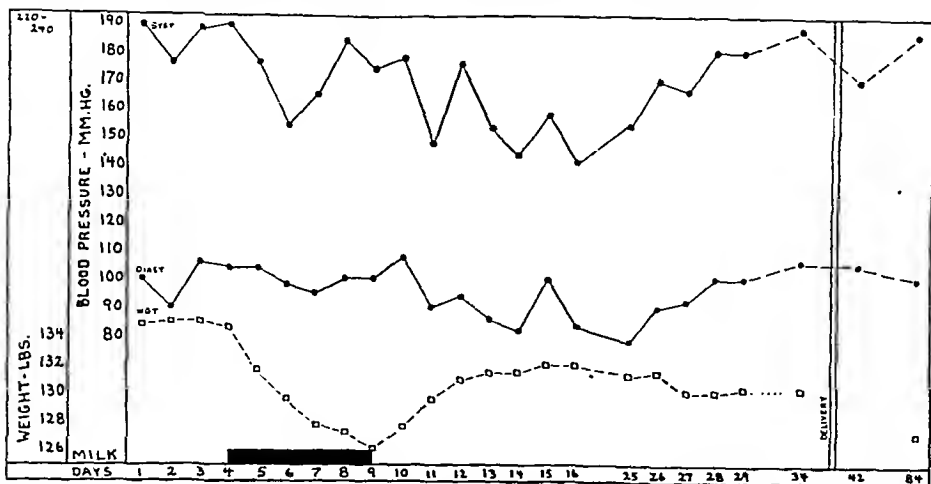


FIG. 2.—Lack of effect of milk diet on blood pressure in case (50) of essential hypertension. Note the slow decline in blood pressure during the first 25 days unrelated to changes in weight; the spontaneous rise in the last 10 days of gestation without gain in weight, and that postpartum the blood pressure was as high as during pregnancy.

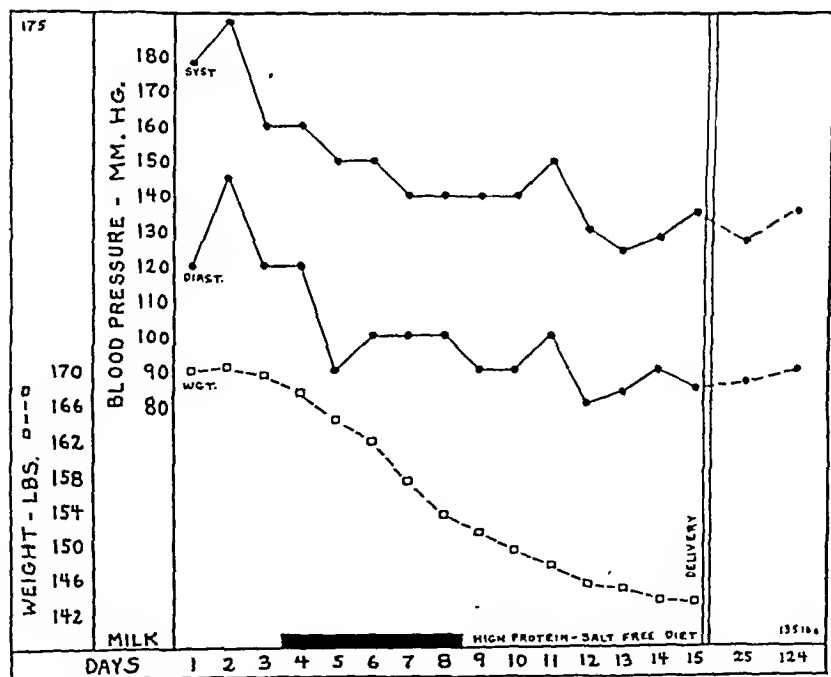


FIG. 3.—Marked fall in blood pressure during milk diet in severe case (60) of true "toxemia" of pregnancy. Note continued normal blood pressure and further weight loss while the patient received a diet containing 150 gm. protein and essentially no salt, and that the blood pressure remain normal postpartum. (In order to show the total loss of 27 pounds in 12 days the weight scale in this figure is smaller than in the other figures.)

Following the period on skim milk these women received a diet which was essentially as free of sodium as practical, which consisted of 150 gm. protein, 100 gm. carbohydrate, and 100 gm. fat. In no instance was there any significant gain in weight on this diet. The arterial blood pressures remained down. Symptoms did not reappear. Albuminuria remained unchanged or decreased further. Parturition and the puerperium were uneventful. Final examinations made postpartum showed normal blood pressures and urines free of albumin.

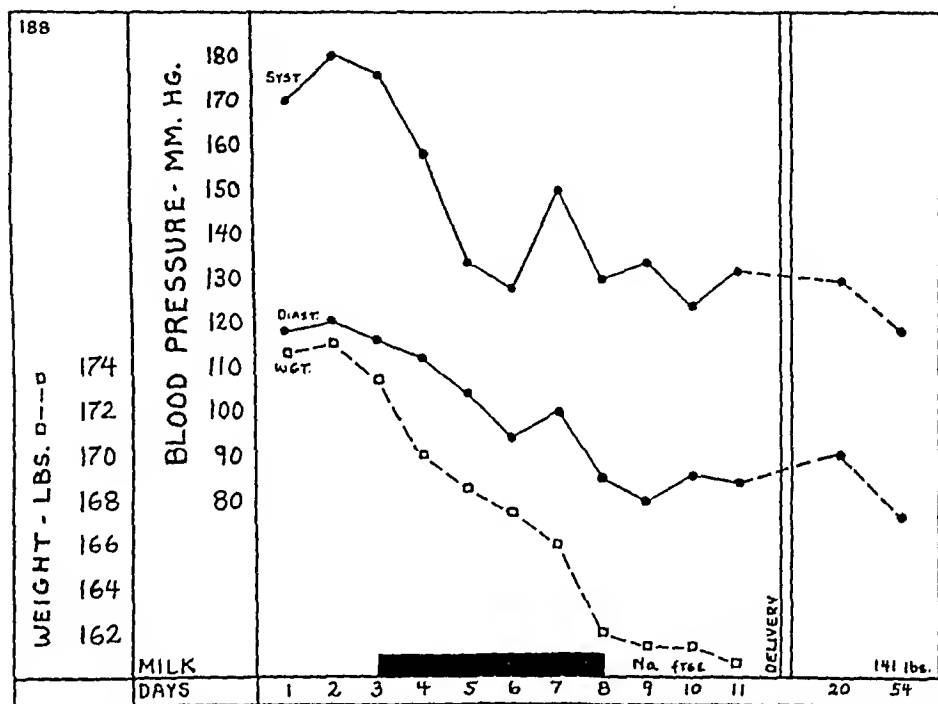


FIG. 4.—Marked fall in blood pressure during milk diet in severe case (58) of true "toxemia" of pregnancy. Note that neither weight nor blood pressure rose while the patient received a diet containing essentially no salt following the milk régime and that the blood pressure remain normal postpartum.

It thus appears that in 10 women with true "toxemia of pregnancy" the plasma protein levels were such that the limitation of sodium intake by means of a milk diet resulted in a marked loss of retained water, preëclamptic symptoms disappeared, the arterial blood pressure fell, and albuminuria diminished.

Discussion. The observations reported here, together with those previously noted,³ indicate that arterial hypertension and symptoms of preëclampsia in true "toxemia of pregnancy" result from undue water retention conditioned by hypoproteinemia. When the plasma proteins are sufficiently low, so that water retention of significant magnitude may be induced by sodium salts, the arterial blood pressure rises and preëclamptic manifestations may appear,^{3c,d} and con-

versely when water retention can be eliminated by acidifying diuretics^{3d} or by a low sodium diet, the arterial blood pressure falls and preëclamptic manifestations disappear. These two sets of observations serve as controls for each other. It is hardly conceivable that hospitalization or spontaneous fluctuation could have been responsible for the rise in blood pressure previously reported in 10 pregnant women given sodium,^{3d} the fall in blood pressure in the 10 pregnant women deprived of sodium here recorded and the fall in blood pressure hitherto noted^{3d} in the 3 given ammonium chloride.

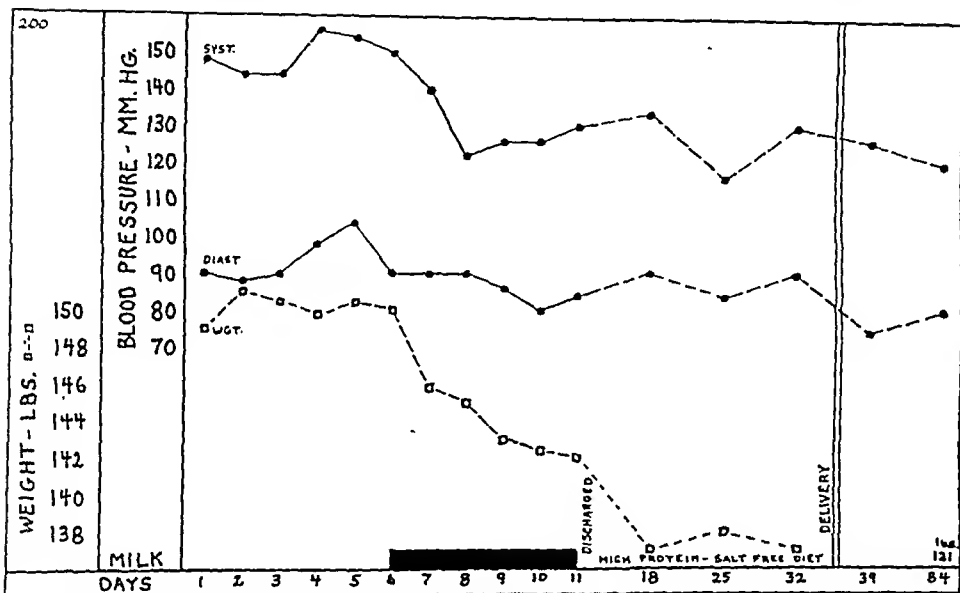


FIG. 5.—Marked fall in blood pressure during milk diet in moderately severe case (55) of true "toxemia" of pregnancy. Note the stationary weight and blood pressure during the control period before the milk régime was commenced, and that the weight remained down and the blood pressure normal during the last 3 weeks of gestation while the patient received *at home* a diet containing 150 gm. protein and essentially no salt; postpartum the blood pressure remained normal.

Furthermore, just as it has been shown previously that sodium salts do not produce increases in hypertension in pregnant women when the plasma protein levels are such that marked water retention does not occur,^{3c,d} it has now been demonstrated that in similar patients a low sodium intake does not result in a fall in arterial blood pressure.

It therefore appears that the response to sodium administration or withdrawal may serve as a means of differentiating between the hypertension observed in true "toxemia of pregnancy" and that of vascular or renal disease in which the pregnancy is but an episode. However, if the plasma protein concentration is exceedingly low, the withdrawal of sodium may have little if any effect on water

retention. This is true in non-pregnant individuals as well as in pregnant women. *Under these circumstances sodium withdrawal has no significant effect upon the arterial blood pressure even though the patient has true "toxemia."*

There is reason to believe that arterial hypertension in general, whether this be due to vascular disease, renal disease, coarctation of the aorta, or "toxemia of pregnancy" is due to arteriolar constriction, either in the form of actual organic change in the arteriolar wall or of spasm. The temporary nature of the hypertension in "toxemia" suggests that spasm is responsible. However, discussion of the mechanism of arteriolar constriction in "toxemia" of pregnancy is beyond the scope of this paper. The fact remains that

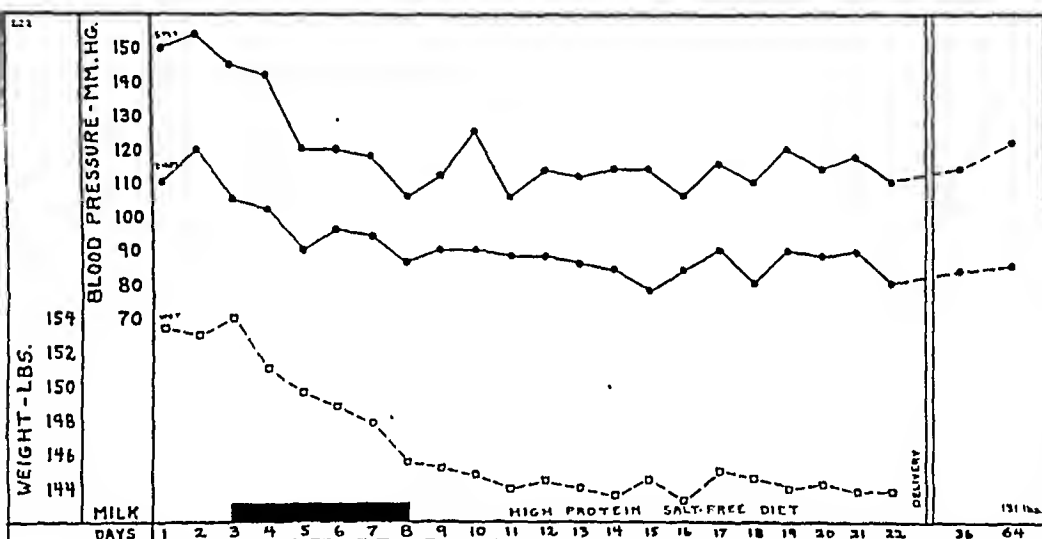


FIG. 6.—Fall in blood pressure during milk diet in moderately severe case (56) of true "toxemia" of pregnancy. Note that the weight remained down and the blood pressure normal during the last 3 weeks of gestation while the patient received a diet containing 150 gm. protein and essentially no salt; postpartum the blood pressure remained normal.

arterial hypertension in this condition is responsive to changes in water balance. Why some patients may have rather marked water retention without arterial hypertension can not be stated at this time. In a number of instances marked water retention has been observed for a period of several weeks before arterial hypertension appeared and in others parturition has supervened without hypertension ever manifesting itself. Whether these women would have eventually developed hypertension had pregnancy continued longer cannot be said. Although there is no evidence for such a belief it is possible that some individual or constitutional susceptibility to hypertension is necessary in order that water retention may produce hypertension during pregnancy.

All of the patients diagnosed as true "toxemia" in this series continued to have normal blood pressures when reexamined from 6 weeks to 4 months after parturition, although albuminuria persisted postpartum in some patients for as long as 2 months before disappearing. Although a number of women who have had eclampsia have been examined as late as 15 years afterward without showing any evidence of vascular or renal disease, many others show definite evidence of such abnormalities. In most instances in which data were available it was found that these women had had vascular or

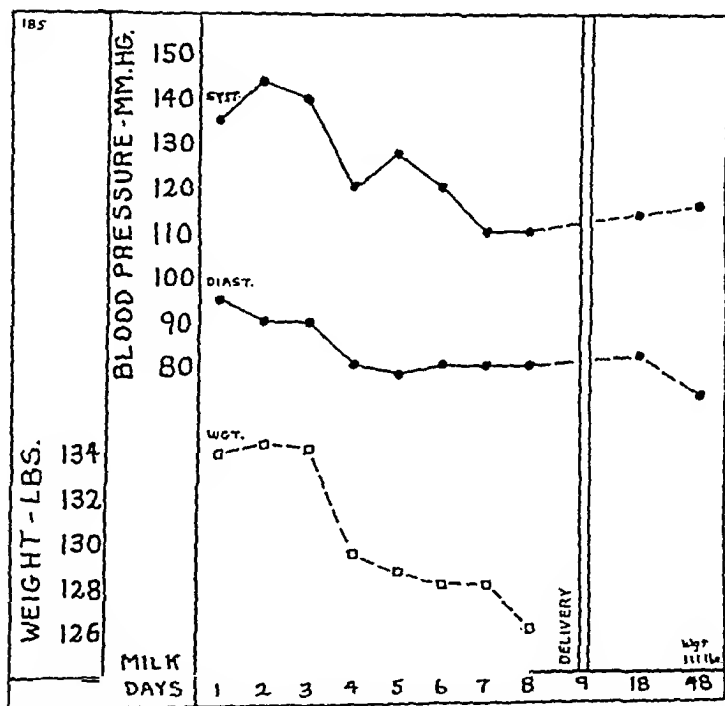


FIG. 7.—Fall in blood pressure during milk diet in mild case (57) of true "toxemia" of pregnancy. Note blood pressure continued normal postpartum.

renal abnormalities prior to pregnancy, and hence were not suffering from true "toxemia" of pregnancy at the time they had convulsions. However, it is easily conceivable that prolonged "toxemia" may result in permanent renal or vascular damage although in none of approximately 80 patients with true "toxemia" has this been observed. There is also little doubt that the syndrome of "toxemia" may be superimposed upon chronic vascular or renal disease or may complicate acute pyelonephritis in pregnancy. In the former instance one would obviously have evidence of vascular or renal damage prior to pregnancy with an exacerbation of manifestations

during gestation and a return postpartum at best only to the pre-pregnant state.

The absence of an effect of a low sodium intake on essential arterial hypertension in pregnancy may be compared to similar observations in non-pregnant subjects with this condition,^{1,2}

It is to be remembered that although a low sodium régime may free the patient of retained water, result in a fall of arterial blood pressure to normal and cause headache, drowsiness, vertigo, and visual disturbances to disappear, such a régime does not alter the fundamental disturbance: hypoproteinemia. These patients remain in unstable equilibrium as long as the plasma colloid osmotic pressure remains at a level at which it is constantly in danger of being overbalanced by the intracapillary hydrostatic pressure. "Cure" cannot be effected unless the plasma proteins can be caused to return to normal. Since "toxemia" occurs late in pregnancy, when fetal demands for protein are large, and since hypoproteinemia probably signifies not only a low plasma protein level but also a depletion of the organism's reserve stores of protein, one must not expect a rapid increase in plasma protein values during the remainder of gestation even with intensive protein feeding. It is possible that the intravenous infusion of concentrated plasma protein ("lyophile" serum) may be of value. However, any procedure which alters the blood volume of such patients may upset their unstable equilibrium and precipitate serious results.

A question which inevitably must arise is whether non-pregnant individuals with similar hypoproteinemic edema show the same phenomena regarding blood pressure as do these women. It is true, of course, that the usual type of non-pregnant patient with hypoproteinemia seen in American hospitals suffers from cirrhosis, nephrosis, anemia, tuberculosis, colitis or other debilitating disease which may alter the reactivity of his vascular system. However, it appears probable that certain peculiarities of the pregnant state itself may be responsible for this unusual behavior of the vascular system to water retention. Some of the *known* physiologic alterations which are present in pregnancy are an increased blood volume, an increased cardiac output, a moderate elevation of venous pressure, and probably moderate mechanical pressure by the enlarged uterus on the ureters and on the renal veins. Although various tests fail to reveal any consistent changes in renal function in "toxemia" of pregnancy the fact that albuminuria is generally present in itself indicates that there is a disturbance of the kidney even though histologic examination fails to reveal anything more than cloudy swelling. The real nature of this disturbance and its possible relationship to the occurrence of hypertension as a result of water retention are unknown. The rôle of hormonal changes in pregnancy is so little understood that discussion is unwarranted. However, the observa-

tion that, in true "toxemia" parturition may be followed by diuresis, loss of edema, decrease in blood volume, and increase in plasma protein concentration before there has been time for much actual regeneration of plasma protein, speaks for the belief that some phenomena normally occurring in pregnancy are involved in the response to water retention.

Since hypoproteinemia is the factor which permits the development of the condition of true "toxemia," adequate prenatal care must include attention to this. Although disturbances of absorption, assimilation, manufacture and urinary loss of protein may be involved, it appears that the chief cause of hypoproteinemia in pregnancy lies in an inadequate dietary intake of protein, especially in view of the increased demands for protein for the developing fetus and also for the maternal organism. It is therefore of paramount importance that the diet in pregnancy contain more, not less, protein than an adequate diet for non-pregnant subjects.

Conclusions. 1. Arterial hypertension in pregnancy due to pre-existing primary vascular or renal disease is not influenced by alterations in water balance.

2. True "toxemia" of pregnancy is the result of undue water retention conditioned by hypoproteinemia.

3. Arterial hypertension and preëclamptic manifestations such as edema, headache, vertigo, drowsiness, and visual disturbances, in the true "toxemia" of pregnancy may be relieved by measures which eliminate undue water retention.

4. Study of the behavior of pregnant women with hypertension after changes in water balance may serve to differentiate true "toxemia" from primary vascular and renal disorders.

5. A diet low in sodium has been shown to be one successful way to decrease or eliminate signs and symptoms of true "toxemia" of pregnancy.

6. The development of true "toxemia" of pregnancy can probably be prevented by maintaining the pregnant woman's plasma proteins at a normal level by adequate diet.

Since this manuscript was submitted for publication corroborative results have been obtained in 25 additional cases.

The writer is indebted to Dr. F. H. L. Taylor and Miss Margaret Adams for carrying out the chemical determinations reported in this paper.

This work was made possible through the coöperation of the visiting surgeons and house staff of the Obstetrical Service of the Boston City Hospital, to whom the writer acknowledges his indebtedness.

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OBSERVATIONS ON REFERRED PAIN OF CARDIAC ORIGIN.*

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THE most commonly employed objective test for the diagnosis of angina of effort is the exercise tolerance test. Several investigators have been successful in inducing an anginal attack^{4,6} by the use of exercise on a standard stairs or by hopping on one foot. This method has failed to give as many positive tests in our hands (Katz and Korey²) as reported by others.^{4,6} The use of epinephrin⁶ or anoxemia⁷ to induce an anginal attack we have found to be too unreliable and hazardous.³ We have developed a new method, simple in its application and less hazardous to the patient, which gave positive findings in many more patients than did the exercise tolerance test. This test consists of inflating an ordinary blood pressure cuff placed on the left arm above the elbow to 50 mm. of mercury above the systolic blood pressure reading. The inflation is continued for five minutes or until cardiac pain is elicited from the patient who does not anticipate such pain. The latter was considered a positive cuff test; its absence constituted a negative cuff test.

The cuff test was tried first on 25 control patients, 40 to 55 years of age, in whom no evidence of heart disease was present. The test was negative in all, the patients complaining only of tingling and pain in the arm distal to the inflated cuff.

The cuff test was then tried on 93 patients of whom 24 had a definite clinical story of angina pectoris, 39 had a questionable clinical story and the remaining 30 had heart involvement but no clinical history of angina. The last two groups included many so-called neurotic patients. The results of the cuff test are shown in Table 1:

TABLE 1.—ANALYSIS OF DATA.

Type of case.	No. of patients tested.	No. of positive cuff tests.	No. of positive exercise tolerance tests.
"Non-cardiac" controls	25	0	*
Heart disease and no angina pectoris	30	0	0
Questionable angina pectoris	39	0	0
Definite angina pectoris	24	19 (80%)	4 (17%)

* No exercise tolerance tests done.

Nineteen positive cuff tests were obtained, all being present in patients in whom a definite clinical history of angina was known. Such a positive cuff test consisted in the development of precordial

* Aided by the A. D. Nast Fund for Cardiac Research.

pain or oppression which the patient stated was similar to the onset of his spontaneous attacks. Only 4 of these patients had a positive exercise tolerance test. In 11 patients in whom pain was produced by the cuff test, nitroglycerin, $\frac{1}{150}$ grain, was given because of the severity of the precordial pain. In 6 of these patients, the cuff was again applied 15 minutes after the attack of pain had been relieved by nitroglycerin, without again eliciting precordial pain. Using the cuff test on the right arm or the right or left legs gave negative results, except in 3 patients who had a definite clinical story of radiation of the pain down the right arm only; in these 3 patients the cuff test was negative on the left arm and legs but positive on the right arm.

The cuff test was repeated on subsequent visits on several patients. While in some it remained negative or positive as on the first visit, in others the test previously positive became negative or *vice versa*. Our data are too scanty to determine the exact cause of this variability, but it would appear to be related to the same emotional and physical factors that lead to the variability in the frequency of spontaneous anginal attacks.

Our experience with this cuff test suggests that while a negative test does not rule out angina pectoris, a positive test is indicative of its presence. It may be found, if further experience confirms these results, that the cuff test may have a place as an aid in the diagnosis of angina pectoris where objective evidence is required to supplement an unreliable history.

As regards the mechanism of a positive cuff test, we may consider three possibilities: 1, A reflex vasoconstriction of the coronary arteries initiated over the segmental distribution of the referred pain; 2, a psychogenic trigger reaction whereby one part of the painful state of angina, the pain in the isehemic arm, sets up in susceptible individuals the entire syndrome; this is in reality a form of so-called conditioned reflex; or, 3, a spatial summation of stimuli coming up from the heart and from the forearm which by using a final common path to the central site of pain perception, convert what otherwise would be subthreshold stimulation for an anginal attack into threshold stimulation. Adrian and his associates¹ have demonstrated the importance of such spatial summation of sensory impulses. Further work is required to differentiate between these possible mechanisms. However, our study has shown, we believe, that one of the variables responsible for an anginal attack is not only the condition of the heart itself, but also that of the sensory regions to which the anginal attack is referred. That this is so has been demonstrated also by the work of Soma Weiss² on the soothing effect of local anesthesia of the region to which pain is referred.

In order to test for the possibility of reflex coronary vasoconstriction, electrocardiograms were taken in a series of 12 patients before and during the carrying out of the cuff test. In 5 patients in

whom the test produced either definite precordial pain, an increase in the existing precordial pain or a sense of pressure over the sternum, the electrocardiogram showed no change during the test, nor was there any change in the 7 patients who developed no precordial pain. It is noteworthy that in one of the patients with a previous coronary occlusion and definite electrocardiographic deformities, complaining of persistent precordial pain before the test was begun, the aggravation of the precordial pain following the cuff test was not accompanied by any change in the electrocardiogram taken during the height of the precordial pain. These results would seem to rule out the possibility that precordial pain following the cuff test was due to a reflex coronary vasoconstriction.

Summary. A method was developed for inducing an anginal attack in susceptible patients with their permission. This was successful in 19 out of 24 patients with definite clinical angina pectoris. It was not successful in producing an anginal attack in any of the 55 cardiac and "non-cardiac" controls nor in any of the 39 patients with doubtful clinical angina pectoris.

The method consisted of producing 5-minute ischemia in the left arm by raising the pressure in a blood-pressure cuff on the arm to 50 mm. Hg above systolic pressure. This cuff test was positive on the right arm and not on the left arm in 3 patients in whom the pain was referred to this arm.

The possible mechanisms involved are discussed. The ability to induce angina in this way serves to emphasize the neuropsychic aspects of the anginal attack and offers another cause for the variability in its occurrence.

We are indebted to Drs. H. Korey, G. Gertz and L. Kaplan for technical assistance.

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PARADOXICAL EMBOLISM.*

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IN 1860, Cohn³ observed that emboli in the right side of the heart can enter the systemic circulation through defects in the cardiac

* Extract from thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M.S. in Medicine.

septum. In 1876, Cohnheim⁴ traced the path of an embolus through an opening in the interatrial septum. An embolus was found in the right cerebral artery and thrombosis of the veins of the lower extremities had occurred. In 1881, Zahn¹⁷ demonstrated a long embolus that had partly passed through a patent foramen ovale. Extensive thrombosis of the iliac veins also was found. Hauser⁷ reported a similar case in 1888. Rostan,¹⁴ in an analysis of 711 postmortem examinations, found the foramen ovale occluded by an embolus in 3 instances and he expressed the opinion that in 7 cases the embolus found in the systemic circulation had passed through a patent foramen ovale. He called this condition "crossed embolism." It was von Reeklinghausen who suggested the term "paradoxical embolism." There have been reports by Ohm,¹² Versé¹⁶ and Beattie² similar to those mentioned.

Abbott,¹ after analyzing 1000 cases of congenital heart disease in which necropsy had been performed, reported 12 cases of paradoxical embolism associated with patency of the foramen ovale, inter-ventricular septum, and ductus arteriosus. In 1935, Hirschboeck⁸ reported a case with a review of the literature. In 1936, Neely,¹¹ and also Jones,⁹ added a similar case.

Koritschoner¹⁰ recorded a case with bibliography but he did not include the cases of Neely and Hirschboeck. He did, however, refer to 2 cases not included in other bibliographies. His statement that 12 cases had been recorded would seem inaccurate but, adding the 2 cases which he omitted, and that of Jones, brings the total to 15.

When pulmonary embolism occurs, it usually follows thrombosis of the systemic veins. Less frequently it is associated with thrombi in the right side of the heart and rarely it is attributable to primary tumors of the heart or to tumor fragments which have invaded the systemic veins.

Emboli of the systemic circulation have many possible sources. They may be dislodged from thrombi in the left side of the heart, associated with disease of the aortic or mitral valves, or from mural thrombi overlying a myocardial infarct or primary tumor. Emboli may arise also from fragments of atheromatous ulcers or from a region of aneurysmal dilatation of the aorta or large arteries. The pulmonary veins occasionally transport emboli from a diseased lung to the left side of the heart. This is particularly true of pneumonia, abscess and gangrene, tuberculosis and tumors. Emboli may arise in the systemic veins or right side of the heart and cross through a patent foramen ovale to the systemic arterial circulation.

As Gross⁵ and others have shown, the pressure in the left atrium is sufficient to make the valvelike flap over the foramen ovale competent, but conditions which reverse the existing pressures cause incompetence and make it possible for emboli or blood to flow from the right atrium directly into the left atrium.

Haggart and Walker,⁶ by observing the effect of graded occlusion

of the pulmonary arteries on the pulmonic and systemic circulation, have demonstrated that sudden occlusion of the left branch of the pulmonary artery causes an immediate rise in pulmonary pressure, averaging about 29%, and following total pulmonary occlusion, the pulmonary pressure increases rapidly, 121 to 267%. At the same time there was an immediate fall in the systemic arterial blood pressure. This coincidence allows the flow of a current of blood from the right atrium to the left atrium, provided the foramen ovale is patent. Thompson and Evans¹⁵ concluded that more than a third of the pulmonary circulation must be occluded before paradoxical embolism can occur. They also stated that if the circulation is depleted more than 50%, death usually occurs within 10 to 30 minutes. In about 50% of the cases "crossed emboli" are preceded by the occurrence of pulmonary embolism; but it is not to be assumed that the presence of a patent foramen ovale with pulmonary embolism always will result in paradoxical embolism.

Six cases of paradoxical embolism are reported in this series. In each case paradoxical embolism was preceded by pulmonary embolism; 3 patients died suddenly and 3 survived long enough for infarcts to develop in other organs. Major surgical operations were performed in 5 cases and 1 was strictly a medical case. In each case, postmortem examination revealed an embolus in transit through the foramen ovale. The average age was 54 years; 3 patients were women and 3 were men.

In addition, a case is reported in which a cerebral abscess developed, probably at the site of a previous paradoxical embolism.

Case Reports. CASE 1.—An obese white man, aged 45, was operated on for subacute cholecystitis with cholelithiasis. Seven days postoperatively, pain developed in the muscles of the calf of the right leg and there was some tenderness over the right anterior saphenous vein. Four days later there occurred a sudden onset of marked pulmonary edema, productive cough, profuse perspiration, and labored respirations with moderate cyanosis. Seven days later pain developed in the right side of the thorax; the pain was exaggerated by breathing. This episode was followed by grayish pallor and profuse sweating. The patient's condition gradually became worse and he died 21 days after operation. *Necropsy* revealed pulmonary embolism and an embolus extending through an anatomically patent foramen ovale; also there were infarcts of the left kidney (paradoxical embolism). The embolus that passed through the patent foramen ovale was 10 cm. long and 5 mm. in diameter (Fig. 1).

CASE 2.—An obese white woman, aged 62, was operated on for subacute, perforating cholecystitis with stones. Her course was uneventful until the 12th postoperative day when pneumonia developed in the lower lobe of the right lung. On the 16th day, she experienced severe substernal pain with evidence of shock and delirium. On the 20th day, right hemiplegia was evident. Death occurred on the 23d postoperative day. *Necropsy* revealed thrombosis of the left posterior cerebral artery, thrombosis of the right auricular appendage, infarction of the right lung, thrombosis of the left pulmonary artery (embolism questionable). The foramen ovale was patent and a clot was found extending through the opening.

CASE 3.—An obese white man, aged 56, was operated on for a suspected ulcerating prepyloric lesion. Two days after operation respiratory infection developed but the patient recovered; 8 days later pain developed in the right anterior part of the thorax. The pain became more severe and was followed by cyanosis. The man rallied slightly but then suddenly became worse and death occurred 12 days after operation. *Necropsy* revealed pulmonary embolism and infarction of the right lung. There was a patent foramen ovale with an embolus extending through it from the right auricle into the left auricle. There were also multiple infarcts of the kidneys.



FIG. 1.—Patent foramen ovale with an antemortem embolus extending through it. View of the left auricle.

CASE 4.—A white woman, aged 56, was operated on for a peptic ulcer. Her course was uneventful until 7 days after operation when she had several attacks of stabbing pain in the right side of the thorax followed by the production of bright red sputum. Two days later she suddenly experienced thoracic pain and this was followed by cyanosis and death. *Necropsy* revealed bilateral pulmonary embolism arising from thrombosis of the iliac veins and inferior vena cava. There was an embolus in the right auricle which projected through a patent foramen ovale. It extended a distance of 1.5 cm. into the left auricle.

CASE 5.—A white man, aged 48, was operated on for carcinoma of the rectum. Convalescence was satisfactory until 17 days after operation when pain, swelling, and tenderness developed over the left femoral vessels. On the 20th postoperative day he had several attacks of dyspnea with pain in the thorax; these symptoms were followed by sudden death. *Necropsy* disclosed, in addition to pulmonary embolism, an embolus 8 cm. in length in the right auricle, projecting through a patent foramen ovale into the left auricle.

CASE 6.—An obese white woman, aged 54, who gave a history of excessive thirst and urination for 6 weeks previously, had been treated for diabetes mellitus. Acidosis was controlled by administration of insulin and fluid and by diet. Two days after her admission, while she was sitting up in bed, she suddenly became dyspneic and cyanotic, and died. *Necropsy* revealed a pulmonary embolus and also an embolus in the right auricle which projected for a distance of 3 cm. into the left auricle, through a patent foramen ovale.

Diagnosis and Prognosis. The diagnosis of paradoxical embolism while the patient is living is made with reservation and is subject to criticism. However, in the presence of venous thrombosis followed by pulmonary embolism and recovery, together with evidence of infarction in other organs, one is justified in suspecting that crossed embolism has occurred. If the acute attack is succeeded by cerebral symptoms, one may consider the diagnosis more positively.

Prognosis depends on the course during the period immediately following the acute episode. The prognosis is almost always unfavorable.

Sequelæ. As a sequel of paradoxical embolus, brain abscess has been reported. Rabinowitz, Weinstein and Marcus¹³ reported a case which they regarded as one of paradoxical brain abscess complicating the tetralogy of Fallot. In a review of the literature, they could find 10 cases besides their own; 6 of the 10 cases had been presented by Abbott and Beattie. They concluded that paradoxical abscess is more common in association with interventricular septal defects than in association with interatrial defects, particularly when there is dextroposition of the aorta. The sudden onset of cerebral symptoms in a case of congenital heart disease, particularly when there is a septal defect, should make one suspicious of paradoxical brain abscess.

Following is a report of a case in which a paradoxical cerebral abscess was suspected:

CASE 7.—A white woman, aged 39, had been examined at the clinic for the first time when she was 19. At that time a diagnosis of congenital heart disease had been made on the basis of cyanosis and clubbing of fingers since childhood, with marked palpitation and dyspnea on exertion. Physical examination had revealed moderate cyanosis of the lips and fingers, with clubbing. The heart was reported to have been slightly enlarged and a systolic murmur had been found at the apex. In the 20 years since her first admission, she had been often seen because of dyspnea and palpitation. At the examination made when she was 39, there was little change in her cardiac condition. Roentgenograms gave evidence of moderate cardiac enlargement, particularly in the region of the conus. The electrocardiogram demonstrated right ventricular preponderance. Studies of the blood indicated a mild compensatory polycythemia. The complaint made on her admission at the age of 39 was that, 1 week before, a respiratory infection had developed. Three days after its onset, she had noticed numbness of her right hand and of the right side of her face, accompanied by twitching and transient swelling of the right arm, and a sense of constriction around her heart. Three similar attacks had taken place within the next 2 weeks. Because of localizing neurologic symptoms and signs, temporoparietal

exploration and decompression were performed. Death occurred on the 13th postoperative day.

Necropsy revealed an abscess in the left cerebrum. The heart weighed 310 gm. There was a patent foramen ovale, 2.5 cm. in diameter, an old thrombus in the pulmonary artery with marked arteriosclerosis and moderate dilatation of the pulmonary artery, and moderate hypertrophy of the right ventricle.

TABLE 1.—SUMMARY OF REPORTED CASES.

Case.	Age, yrs.	Sex.	Clinical diagnosis.	Anatomic diagnosis.
1	45	Male	Subacute cholecystitis with cholelithiasis	Pulmonary embolism through patent foramen ovale
2	62	Female	Subacute perforating cholecystitis and cholelithiasis	Thrombosis posterior cerebral and left pulmonary artery; embolus through patent foramen ovale
3	56	Male	Ulcerating prepyloric lesion	Pulmonary embolism; infarction right lung and both kidneys; embolus through patent foramen ovale
4	56	Male	Peptic ulcer	Bilateral pulmonary embolism; thrombosis iliac veins and inferior vena cava; embolus through patent foramen ovale
5	48	Male	Carcinoma of rectum	Pulmonary embolism; embolus through patent foramen ovale
6	54	Female	Diabetes mellitus	Pulmonary embolism; embolus through patent foramen ovale
7	39	Female	Congenital heart disease; brain abscess	Abscess left cerebrum; patent foramen ovale

Comment. The cases reported (tabulation) illustrate one of the results of what is referred to, generally, as a benign cardiac malformation, that is, the patent interauricular septum. Although paradoxical embolism is interesting from the pathologic point of view and is usually termed a pathologic curiosity, it is not without clinical interest. The diagnosis of a paradoxical or crossed embolism rarely is made during the life of the patient because there are few indicative signs or symptoms. Furthermore, death from pulmonary embolism usually occurs so rapidly that there is little time for evaluation of the presenting clinical syndrome. However, the diagnosis may be suggested by the presence of pulmonary and congenital heart disease. Careful appraisal of all the signs and symptoms, with the thought of paradoxical embolism in mind, may aid in a more frequent antemortem diagnosis. Even without the clinical diagnosis of congenital heart disease, the syndrome of pulmonary embolism followed by multiple infarction in the organs supplied by the systemic circulation should suggest that paradoxical embolism may have occurred. In all of the 7 cases reported there were defects of the interauricular septum, but in only 1 were there signs or symptoms of congenital heart disease. Paradoxical brain abscess is the rarest complication of paradoxical embolism.

Conclusion. The diagnosis of paradoxical or crossed embolism is rarely made while the patient is alive. There are few signs or symp-

toms indicative of such a process. However, the diagnosis may be suggested by the presence of pulmonary embolism and congenital heart disease. In all of the 7 cases reported, there were interatrial septal defects, but in only one were there signs or symptoms of congenital heart disease.

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RADIOLOGIC MEASUREMENTS OF THE APICO-BASAL RELAXATION OF THE LUNG DURING ARTIFICIAL PNEUMOPERITONEUM TREATMENT.

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DURING recent years publications have appeared in the medical literature in which the problem of treating pulmonary tuberculosis by artificial pneumoperitoneum was discussed.^{1a,7} Subsequent clinical observations seem to confirm the assumption that repeated injections of oxygen or air into the peritoneal cavity exert a favorable effect upon certain types of tuberculous lesions of the lung.^{1b,c,2-6} The favorable influence is attributed to the elevated position of the diaphragm, which, in turn, causes a pulmonary relaxation. It is reasonable to assume that a sufficient degree of pulmonary relaxation induced by pneumoperitoneum might lead to mechanical, circulatory, and immunologic changes in the lung similar to that which follow surgical paralysis of the phrenic nerve, or artificial pneumothorax.

With the patient in the upright position the injected gas occupies the area underneath the diaphragm. The fluoroscopic or roentgenographic appearance of the gas suggests a rather marked upward displacement of this muscle. I^{1b} have pointed out in a previous publication that the area occupied by the gas does not signify a corresponding upward displacement of the diaphragm, but it is

partly made up by a descent of the subdiaphragmatic organs. Because of the fact that there is no report in the literature dealing with the accurate measurement of the elevation of the diaphragm in a series of cases treated by pneumoperitoncum, I wish here to present data related to this question.

Method. A group of 40 patients who were receiving pneumoperitoneum treatment for their pulmonary tuberculosis was studied roentgenologically. Of these, 11 were in the moderately advanced stage and 29 in the far-advanced stage (Nat. Tuberc. Assn. classification). Roentgenograms taken before and during the treatment were compared. The amount of injected air at each treatment varied from 500 to 1000 cc. Measurements were made in 32 cases after 1 treatment; in 1 case after 2 treatments; in 7 after 3; in 6 after 4; in 2 after 5; in 8 after 6; in 2 after 7; in 2 after 8; in 7 after 10; in 1 after 11; in 3 after 12; in 1 after 14; in 2 after 15; in 4 after 16; in 1 after 20; in 4 after 22; and in 1 after 23 treatments. The treatments were given at weekly intervals at the beginning and 2 weeks apart when the pneumoperitoneum was well established. Roentgenograms were taken at maximum inspiration and at maximum expiration in every instance. Thus, including the films taken before treatment, 248 chest films were measured and analyzed. The exposure was made with the patient in the upright position, from a distance of 6 feet. The apico-basal diameter was measured from the highest point of the apex of the lung to the highest point of the corresponding dome of the diaphragm.

The upward displacement of the diaphragm is influenced by several factors: 1, the tonicity and integrity of the diaphragm (diaphragmatic atony, presence or absence of adhesions); 2, the tonicity of the abdominal wall (inherent anatomic status, reflex relaxation or contraction in response to the injection of air); 3, pathologic changes in or surgical status of the lung (contracting, fibrosing tuberculosis, "spontaneous" paralysis of the diaphragm, massive or partial atelectasis, artificial pneumothorax, surgical paralysis of the phrenic nerve, thoracoplasty, large pleural effusion); 4, the type of breathing (there is a greater tendency toward collection of air underneath the diaphragm in individuals with distinctly thoracic type of breathing than in the thoracic-abdominal or abdominal type of breathing); 5, the amount of air injected.

Following the first pneumoperitoneum treatment there was no change in the position of the diaphragm (2 mm. or less), in 8 of the 32 cases in this group. The maximum elevation of the right and left dome of the diaphragm on inspiration and expiration is given in Table 1.

The figures representing the actual rise of the diaphragm compare favorably with the elevation of the diaphragm after phrenic nerve block. I¹ have studied a comparable group of 30 patients who had a surgical paralysis of the phrenic nerve by the same roentgenologic method and found that the rise after phrenic operation was, on inspiration, 4 cm. or more in 4 (of these there was only 1 as high as 6.3 cm.); 3-3.9 cm. in 10; 2-2.9 cm. in 4; 1-1.9 cm. in 7; less than 1 cm. in 2; and it was absent in 3; in expiration the rise was 4 cm.

or more in 2 (the maximum was 4.5 cm.), 3-3.9 cm. in 1; 2-2.9 cm. in 7; 1-1.9 cm. in 11; less than 1 cm. in 8; and it was absent in 1.

TABLE 1.—MAXIMUM ELEVATION OF THE DIAPHRAGM IN CENTIMETERS AFTER VARYING NUMBER OF PNEUMOPERITONEUM TREATMENTS.

Number of cases		32	1	7	6	2	8	2	2	7	1	3	1	2	4	1	4	1
Number of treatments		1	2	3	4	5	6	7	8	10	11	12	14	15	16	20	22	23
Right	Inspiration	4.2	3.2	2.6	2.3	5.6	3.2	4.1	4.3	5.1	1.8	5.8	3.5	3.5	2.4	5.2	6.0	7.3
	Expiration	4.5	3.1	2.0	2.6	3.6	4.8	2.6	4.7	5.2	1.6	5.3	4.4	6.1	2.7	4.0	4.9	5.8
Left	Inspiration	4.2	2.7	3.2	2.5	3.6	2.5	4.2	3.8	3.8	2.0	6.1	4.0	3.2	3.2	2.5	6.1	5.4
	Expiration	2.8	3.5	3.0	2.4	3.0	4.0	3.1	5.1	3.0	2.0	5.8	4.3	6.4	2.0	5.7	4.8	5.6

TABLE 2.—MAXIMUM INDICES OF APICO-BASAL RELAXATION REPRESENTING THE PERCENTAGE BY WHICH THE ORIGINAL APICO-BASAL DIAMETERS WERE REDUCED.

Number of cases		32	1	7	6	2	8	2	2	7	1	3	1	2	4	1	4	1
Number of treatments		1	2	3	4	5	6	7	8	10	11	12	14	15	16	20	22	23
Right	Inspiration	18.6	15.2	11.3	10.0	25.0	19.9	19.5	20.5	30.0	8.5	20.7	14.8	15.7	18.1	25.6	23.6	32.8
	Expiration	18.0	15.5	11.2	12.0	17.5	22.6	11.2	23.5	32.6	8.3	27.2	19.0	31.5	17.5	22.1	22.0	30.2
Left	Inspiration	18.3	12.0	12.5	10.6	13.8	25.2	17.5	17.0	16.9	9.6	25.3	15.6	13.6	16.8	13.1	27.0	22.9
	Expiration	9.4	10.8	12.2	11.1	13.7	22.8	11.0	24.6	20.3	10.1	30.0	16.8	25.7	17.4	31.3	25.0	27.1

A better estimate of the upward displacement of the diaphragm can be gained when one compares the decrease in the apico-basal distance with the length of the apico-basal diameter before treatment. The quotient representing this relation can be designated as the index of apico-basal relaxation. It is calculated according to the following formula: Decrease in the apico-basal diameter divided by the original apico-basal diameter and multiplied by 100. For example, in Case 10 the decrease in the apico-basal diameter was 4.2 cm. on the right side on inspiration after the first treatment; the original apico-basal distance was 22.5 cm.; the index of apico-basal relaxation was $(4.2/22.5) \times 100$ or 18.6. In other words, the apico-basal diameter was reduced by 18.6%.

A comparison was made between the degrees of apico-basal relaxation in inspiration and in expiration. The analysis of the right and left lungs in 84 instances comprises 168 measurements. The index of apico-basal relaxation was equal during the two respiratory phases in 11; it was greater on expiration than on inspiration in 100, and it was smaller on expiration than on inspiration in 57 measurements.

The indices of apico-basal relaxation on the more involved and on the "good" side were compared in 18 instances, including cases that

had 10 treatments or more. It was found that the relaxation of the two sides was approximately equal on inspiration and expiration in 4, on inspiration in 1 and on expiration in 5. The relaxation on the "good" side was greater than on the diseased side in both respiratory phases in 1, on inspiration in 7, on expiration in 1. The relaxation on the diseased side was greater than on the "good" side in both respiratory phases in 3, on inspiration in 2, and on expiration in 4 instances.

As to the changes in the position of the diaphragm during the course of pneumoperitoneum treatment, some illustrative cases can be cited.

Case Abstracts.—**CASE 1.** E. G., aged 30, male, had a far-advanced pulmonary tuberculosis of $7\frac{1}{2}$ years' duration. The first treatment with the injection of 500 cc. of air caused no elevation of the diaphragm, except a 1.6 cm. rise on the left side during expiration. Following the third treatment with the injection of 600 cc. of air the rise was on the right side on inspiration 0.8 cm. (3.9% of the apico-basal diameter), and on expiration 2 cm. (11.2%); on the left side on inspiration 1.5 cm. (7.8%), and on expiration 2.2 cm. (12.2%). After the injection of 700 cc. of air on the 22d treatment, the rise was on the right side on inspiration 2.4 cm. (11.9%), and on expiration 3.5 cm. (19.6%); on the left side on inspiration 3 cm. (15.7%), and on expiration 3.7 cm. (20.5%).

CASE 2.—G. E., aged 21, male, had a far-advanced pulmonary tuberculosis of $1\frac{1}{2}$ years' duration. First treatment: amount: 500 cc.; rise of right dome of diaphragm on inspiration 1.7 cm. (7.6%), on expiration 0.8 cm. (4.1%); rise of the left dome of the diaphragm on inspiration 0.9 cm. (3.8%), on expiration 0.5 cm. (2.4%). Sixth treatment: amount: 1000 cc.; rise on the right side on inspiration 3.2 cm. (14.4%), on expiration 1.4 cm. (7.2%); on the left side on inspiration 2.7 cm. (11.4%), on expiration 1.8 cm. (8.7%). Twelfth treatment: amount: 1000 cc.; rise on the right side on inspiration 4 cm. (18%), on expiration 1.9 cm. (10%); on the left side on inspiration 3.4 cm. (14.4%), on expiration 3.5 cm. (16.9%). Twenty-third treatment: amount: 1000 cc.; rise on the right side on inspiration 7.3 cm. (32.8%), on expiration 5.8 cm. (30.2%); on left side on inspiration 5.4 cm. (22.9%), on expiration 5.6 cm. (21.7% of the apico-basal diameter).

These cases demonstrate that a substantial and sustained elevation of the diaphragm, and consequently a satisfactory relaxation of the lung, can be produced by weekly injections of air into the peritoneal cavity.

Summary. 1. Comparative measurements and analysis of 264 roentgenograms of the chest, taken before and during artificial pneumoperitoneum treatment of 40 patients, are presented. These data and their evaluation must be interpreted with the qualification that it was impossible to eliminate entirely some differences in the respiratory efforts of the patients, and consequently in the motion of the chest and the diaphragm, when films were taken on repeated occasions.

2. Repeated injections of air into the peritoneal cavity at weekly intervals are likely to cause a sustained elevation of the diaphragm, provided, pathologic changes, such as fixation of the diaphragm by adhesions, or the presence of extensive adhesions between the

convexity of the liver and the lower surface of the diaphragm, do not obviate it.

3. The maximum elevation of the diaphragm induced by pneumoperitoneum was on inspiration 7.3 cm. on the right side and 6.4 cm. on the left side; on expiration 6.4 cm. on both sides.

4. The maximum elevation of the diaphragm by pneumoperitoneum was greater than that observed after surgical paralysis of the phrenic nerve in a comparable group of patients.

5. The maximum reduction in the length of the apico-basal diameter was on inspiration 32.8% on the right side and 27% on the left side, and on expiration 32.6% on the right side and 34.3% on the left side.

Conclusion. Artificial pneumoperitoneum treatment in pulmonary tuberculosis, when given at regular intervals, is capable of inducing a degree of relaxation of the lung that is known to be sufficient to improve the resistance, defense, and repair of the pulmonary tissues, and thus it brings about a condition which is favorable to the healing process of tuberculous lesions.

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DIABETIC COMA REQUIRING AN UNPRECEDENTED AMOUNT OF INSULIN.

REPORT OF A CASE MANIFESTING EXTREME INSULIN RESISTANCE.

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THE case of atypical diabetes mellitus described in this preliminary report was rescued from coma by means of the administration of larger doses of insulin than appear ever to have been given before. The subsequent clinical course in the 5 months to date (January 31, 1938) has been featured by the continued need for daily administration of very large doses of insulin. The largest dose given in 24 hours, on September 27, 1937, was 3250 units of regular insulin, which, I believe, according to a search of the literature, is by far the largest amount ever given to a human subject.

Report of Case. Mr. J. S., Jewish, born in Russia in 1879, first seen September 21, 1937, at the age of 58, is a grocery-store owner who has lived in New York City for the past 31 years. He is married and has

4 children who are living and well. As far as he knows no other member of his family has had diabetes. There was no serious medical or surgical illness in his past history.

At an insurance examination in 1934 a trace of sugar was found in the urine. At that time he weighed 160 pounds. Early in the winter of 1937 symptoms of moderately severe diabetes gradually developed, viz: polyuria, polydipsia and polyphagia. However, as he neglected to seek medical advice, no diagnosis was made or treatment instituted up to the time of hospitalization.

Two days before his first admission to the Gouverneur Hospital on May 14, 1937, the patient complained of a pain in the right groin, and of



FIG. 1.—Mr. J. S., January 20, 1938.

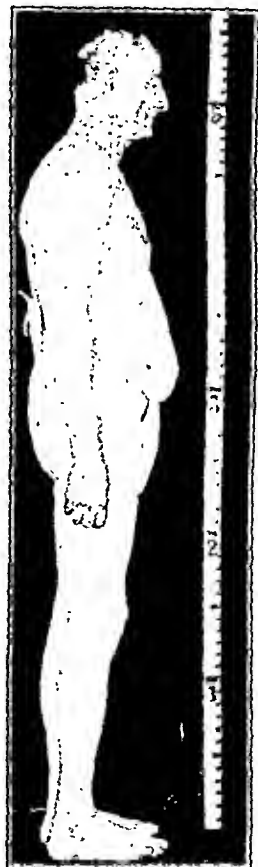


FIG. 2.—Mr. J. S., January 20, 1938.

dysuria. His temperature was found to be 101° F.; the urine showed a few pus cells, 3% of sugar and 2+ acetone. The blood sugar was then 425 mg. %; N.P.N., 27. On admission, his weight was 131 pounds; there was slight costo-vertebral tenderness, and temperature 101° F. The tentative diagnosis was pyelitis. Regular insulin in diminishing doses, starting at 155 units in the first 24 hours, brought the diabetes under control in 1 week, and he was discharged after a 2 weeks' stay in the hospital with the urine free of sugar and acetone and on protamine-zinc insulin, 50 units

in 1 daily dose. The diet on discharge was: C., 200; P., 70; F., 70. His weight was 129 pounds. During the summer he gained weight up to 140 pounds and remained sugar-free on this régime.

Three weeks previous to his second admission on September 13, 1937, a large amount of sugar was again found in the urine, although the patient insists that there had been no "breaks" in his diet. The diet was then further restricted and protamine insulin gradually increased, with the addition of a certain amount of regular insulin, but at the end of a week the sugar had not decreased, and acetone 2+ had appeared in the urine. He was then kept in bed at home for 2 weeks; fluids were forced, and regular insulin was gradually increased up to 260 units in divided doses without any signs of improvement. His weight dropped to 110 pounds in a period of 4 weeks. On the night before readmission, September 14, 1937, clinical signs of marked acidosis were evident, including acetone odor to the breath and marked hyperpnea. He complained that night of severe substernal burning sensation, and vomited once.

Physical examination at the hospital was essentially normal for a man of his age, except for the marked dehydration and the evidences of acidosis. There was no abnormal pigmentation of the skin or mucous membranes, nor any obvious adenopathy. The heart and lungs were normal. The peripheral arteries were moderately thickened and slightly tortuous. There was visceroptosis. The liver was not enlarged but the edge could be felt due to ptosis. There was no evidence of the presence of any abnormal abdominal masses or of ascites. All superficial reflexes were normal. There was no edema of the extremities or elsewhere. The eyegrounds were normal except for evidence of moderate arteriosclerosis. The visual fields were normal. Roentgen ray films of the skull and the chest revealed nothing abnormal. The renal function was apparently entirely normal. Blood sugar was 344 mg. % and CO_2 -combining power of the plasma, 29 vol. %. The routine treatment for pre-coma was instituted, and 440 units of insulin given in the first 24 hours. Fluids in the amount of 8000 cc. were given and the output was 5000 cc. On the next day 1105 units of insulin were given, carbohydrates of about 200 gm.—part by 5% glucose infusion—but the sugar remained 4+ in the urine (6800 cc.) although acetone was absent. During the next 5 days excessive polyuria, high glycosuria, and increasing ketonuria persisted, despite an average daily dose of 900 units, and subjective and objective signs of incipient coma were definitely present on September 21, 1937, when I first saw the patient. Although the CO_2 was 54 on September 17, on September 21 at 8 A.M. it had fallen to 9, and at 12 M., due to the measures instituted, as shown in Table 1, the CO_2 rose to 19.

The essential data of the critical 24 hours from 8 A.M. September 21 to 8 A.M. September 22 will be found in Table 1. It will be noted that glycosuria was controlled, ketonuria diminished, and the clinical condition markedly improved, chiefly due to 5 measures: 1, Very large and frequently repeated doses of insulin;* 2, large amounts of fluid; 3, alkali (sodium bicarbonate); 4, sodium chloride, by vein; 5, cardiac and respiratory specific stimulation.

The essentials of the daily record through October 20, 1937, may be found in Table 3, and it will be noted that the largest dose of insulin was given September 27 to 28, 1937. The details of this single day are shown on Table 2. The reason for administering this large amount was that the

* Through the obliging coöperation of the New York office of Eli Lilly and Company, several thousand units of their U-100 regular insulin were supplied gratis to the patient during the first 2 weeks, and since then E. R. Squibb & Co. have donated from 10,000 to 14,000 units of their U-100 regular insulin every week for 12 weeks, a total to date of 142,000 units.

patient had again begun to show ketonuria as well as the clinical signs of acidosis, despite the large doses of insulin given on the preceding days. He has shown no signs of acidosis since that day (except on one occasion a month later) and was subjectively well and up and about the ward, and discharged, November 5, 1937. He was instructed to take 1700 units of insulin, divided into 4 doses, and a diet of C., 300; P., 100; F., 100. He has since been managed as an ambulant patient, and has been working at his regular occupation.

TABLE 1.—CLINICAL COURSE ON SEPTEMBER 21 AND 22, 1937.

Time.	Insulin, units.	Blood chemistry.		Urine.			Remarks.
		Sugar, mg. %.	CO ₂ , vol. %.	Vol., cc.	Sugar, %.	Acetone.	
Sept. 21.							
12.01 A.M.	100	310	4.0	4+	P., 112; R., 26; acetone on breath, 4+—all day.
2.00 A.M.	100	220	2.0	3+	
6.00 A.M.	100	200	3.0	3+	Vomited; B.P., 140/80.
8.00 A.M.	...	242	9	Stuporous.
10.00 A.M.	50	120	3.5	4+	N.P.N., 26.
12.00 M.	...	238	19	
1.00 P.M.	150	780	4+	4+	Insulin given in 1000 cc. of 5% glucose and physiologic saline.
2.00 P.M.	100	520	4+	4+	Strophanthin, 0.75 mg. IV at 1.45 P.M.
2.45 P.M.	100	
4.00 P.M.	360	4+	4+	Metrazol, 2 cc. IM.
6.00 P.M.	360	4+	4+	Metrazol, 1 cc. IM at 5 and 6 P.M.
							Strophanthin, 0.75 mg. IV at 4 and 6 A.M. Still drowsy; condition unchanged; R., 38.
6.45 P.M.	320	4+	4+	Infusion, 500 cc. 5% NaHCO ₃ at 6.30 P.M.
8.00 P.M.	200	300	4+	4+	Infusion, 200 cc. 5% glucose.
9.00 P.M.	200	300	4+	4+	
9.30 P.M.	320	4+	4+	
10.00 P.M.	200	240	4+	4+	
11.00 P.M.	200	450	4+	4+	4 gm. NaHCO ₃ by mouth at 10.45 P.M.
	1500	4900	Total for 24 hours.
Sept. 22							
12.00 M.	200	180	4+	4+	Restless; respirations labored.
1.00 A.M.	200	450	4+	4+	
2.00 A.M.	200	360	2.0	4+	
3.00 A.M.	200	180	1.8	4+	
4.00 A.M.	200*	160	1.5	4+	
5.00 A.M.	200	180	1.0	4+	
6.00 A.M.	200	120	0.5	4+	
6.30 A.M.	200	120	0.4	3+	Infusions, 500 cc. 10% glucose.
7.00 A.M.	50	Tr.	2+	Condition better, respirations normal.
8.00 A.M.	30	Tr.	2+	Color fair.

Antique figures represent protamine zinc insulin.

* 1800 cc. of normal saline 9 P.M. to 8 A.M. given very slowly by vein and containing all subsequent insulin. Metrazol, 1 cc. IM at 7 and 8 P.M. B.P., 112/50.

The insulin was increased to 2800 units on November 24, 1937, because of ketonuria and symptoms of acidosis on the preceding day on a dosage of 2000 units. This was then reduced on November 26, 1937 to 1400 units in 5 doses.

On December 6, 1937, he took regular insulin as follows: 6 A.M., 600 units; 8 A.M., 400; 11 A.M., 400; 2 P.M., 200; 5 P.M., 200; 8 P.M., 200; 10 P.M., 200. And this was his insulin régime throughout December and the first 2 weeks of January, except for minor variations in dosage. With the diet

remaining the same, the 24-hour urinary sugar would vary from 40 to 90 gm. At the present time he is excreting about 50 gm. and the insulin has been reduced to 700 units, with the following dosage: 6 A.M., 300, and subsequent 4 doses of 100 units Q.4H. up to 10 P.M. His present weight is 142 pounds and he is subjectively entirely well.

The patient was in the Post-Graduate Hospital for a 48-hour period of observation (January 27 to 29). The diet was carefully controlled at C., 300; P., 100; F., 100; and the insulin, 1400 units, given in the same intervals and amounts as he had been taking outside. Table 4 shows the analyses of the divided urine specimens and other relevant data. The

TABLE 2.—CLINICAL COURSE ON SEPTEMBER 27, 1937.

Time.	Insulin.		Urine.				Remarks
	Units.	Route.	Vol., cc.	Sugar, %.	Sugar, gm.	Acetone.	
Sept. 27							
9 A.M.	330	2.0	6.6	0	Bl. sugar, 185; CO ₂ , 59; Cl., 420; N.P.N., 27.
10 A.M.	250	SC	390	2.4	9.5	0	5 gm. NaHCO ₃ by mouth, 1 gm. NaCl by mouth.
11 A.M.	210	3.0	6.3	Tr.	
12 M.	150	SC	300	1.4	5.2	Tr.	1 gm. NaCl by mouth.
1 P.M.	150	SC	300	2.0	6.0	Tr.	
2 P.M.	150	SC	150	2.0	3.0	1+	1 gm. NaCl by mouth.
3 P.M.	150	SC	210	3.3	6.6	Tr.	
4 P.M.	150	SC	270	3.5	9.7	1+	1 gm. NaCl by mouth.
5 P.M.	150	IV	240	3.3	8.2	1+	2 gm. NaCl by mouth.
6 P.M.	150	IV	210	2.8	6.0	1+	1 gm. NaCl by mouth.
7 P.M.	150	IV	120	1.8	3.6	1+	
8 P.M.	150	IV	120	1.9	2.3	Tr.	
9 P.M.	150	SC	150	1.0	1.5	Tr.	
10 P.M.	250	IM	120	0.5	0.6	Tr.	NOTE.—Last day of ketonuria. Patient subjectively well. Diet: C., 180; P., 120; F., 60; divided in 6 meals at 6 A.M., 10 A.M., 2 P.M., 6 P.M., 10 P.M., 2 A.M.
11 P.M.	100	0.2	0.2	0	
12 M.	250	IM	125	0.4	0.5	0	
1 A.M.	120	0.8	1.0	0	
2 A.M.	250	IM	300	0.3	0.9	0	
3 A.M.	120	0.4	0.5	0	
4 A.M.	250	IM	100	0.5	0.5	0	
6 A.M.	250	IM	300	0.1	0.3	0	
8 A.M.	250	SC	200	0.7	1.4	0	
	3250	...	4485	...	82.0	...	
Sept. 28							Total in 24 hours.
9 A.M.	Bl. sugar, 66; CO ₂ , 46.

highest concentration of glucose in the urine is seen to occur between the hours of 7 and 11 A.M. Although there never have been any clinical indications of hyperthyroidism, the basal metabolic rate was 29% above normal.

An attempt was made to determine whether the presence of contra-insulin hormones could be detected in the patient's blood. To this end the serum of the patient and the serum of a non-diabetic case were incubated with insulin for 3 days, and then injected intravenously into fasting rabbits and the blood sugar lowering effect studied. As seen in Table 5, the serum of the patient in this test manifested no contra-insulin activity.

The possible presence of insulin antibodies in the serum of the patient was ruled out by Prausnitz-Kustner passive transfer tests, done by Dr. M. B. Sulzberger and his co-workers. These experiments were performed with ordinary purchasable insulin, as well as with the special pork and the special beef insulins of Lilly. The results proved that there were no passive transfer antibodies to insulin in the serum of the patient.

With the coöperation of Dr. M. Bruger and Dr. C. V. Bailey, a detailed metabolic study was undertaken at the Post-Graduate Hospital, the results of which will be published in a subsequent communication.

TABLE 3.—CLINICAL COURSE IN SEPTEMBER AND OCTOBER.

Date.	Insulin, units in 24 hrs.	Blood chemistry.			Urine.			Remarks.
		Time.	Sugar, mg. %.	CO ₂ , vol. %.	Vol., cc.	Sugar, gm.	Ke- tones.	
Sept. 13	425	...	375	4+	B.P., 160/80.
14-16	1560 (45 hr.)	4+	
16	1105	...	161	...	3000	12	4+	Blood Cl., 420
17	715	...	225	54	4+	B.P., 90/60; acetone breath,
20	785	8 A.M.	242	9	5000	225	4+	4+; P., 120-130.
21	1500	12 M.	238	Tr.	Cl., 60 gm.; NaHCO ₃ , 83 gm. by mouth <i>et seq.</i>
		12 M.	238	19	Tr.	Blood acetone, 78 mg. % with urine acetone negative.
		9 A.M.	153	35	3000	30	Tr.	Diet: C., 180; P., 120; F., 60;
22	2700	1 P.M.	200	64	3800	40	Tr.	in 6 meals; B.P., 140/80.
		Urine Cl. in 24 hours, 10 gm.
23	1220	...	217	63	5500	77	0	Urine Cl. in 24 hours, 8 gm.
		...	200	54	5500	150	0	First mild insulin reaction,
24	2200	1 P.M.	222	36	4500	90	0	2 P.M.
25	1620	8 A.M.	185	59	4300	40	0	Second mild insulin reaction,
26	2440	9 A.M.	66	46	2400	12	...	6 P.M.
27	3250	0	Calcium gluconate begun.
28	1200	2 P.M.	75	0	
		...	224	51	2400	14	0	
29	1800	...	127	...	3200	100	0	
30	2100	0	
Oct. 1	1700	2450	24	0	Diet: C., 260; P., 80; F., 100
2	1450	...	222	39	2400	25	0	mild ins. reac.
3	1300	1800	50	0	Diet: C., 300; P., 100; F., 100
4	1300	1500	78	0	
5	1300	2000	40	0	
		0	Bl. Cl., 440; chol., 174; Ca.,
6	1200	...	247	53	2500	13	0	10.4; P., 4.4.
11	1420	1 P.M.	125	54	1800	45	0	Bl. Cl., 515; pl. Cl., 645; uric
15	1620	1930	38	0	ac., 3.2.
		11 A.M.	280	...	1960	100	0	No insulin reaction since Oct.
18	1600	2 P.M.	283	...	2000	68	0	15.
19	1660	2160	75	0	
20	

TABLE 4.—TWO-DAY OBSERVATION AS IN-PATIENT IN DECEMBER.

1937.	Time of collection.	Vol., cc.	Specific gravity.	Sugar.		Acetone.	Insulin.	Diet.
				%	Gm.			
Dec. 27	7 P.M.—	382	1.023	1.2	4.6	0	1400 units in 7 doses	C., 300; P., 100; F., 100.
28	7 A.M.—7 A.M.	856	1.025	6.7	57.3	Tr.		
	7 A.M.—11 A.M.	235	1.028	5.6	13.2	Tr.		
	11 A.M.—3 P.M.	320	1.028	4.0	12.8	Tr.		
	3 P.M.—7 P.M.	1793	...	6.0	87.9	Tr.		
29	24 hours	135	8.1	...		
	7 A.M.—9 A.M.		

Dec. 28: Insulin, SQ, 500 units at 6 A.M., 300 at 8 A.M., 200 at 10 A.M., and 100 at 1, 4, 7 and 10 P.M.
Dec. 29: B.M.R., +29%; pulse, 88; fasting blood sugar, 306 mg. %.

TABLE 5.—TEST FOR CONTRA-INSULIN ACTIVITY OF SERUMS.
(4.5 cc. serum to which was added 0.5 cc. Insulin U-40 (20 units), incubated for 3 days at 37° C. These sera were then injected intravenously into 2 fasting rabbits and blood sugars done fasting, and at 4-hour, 1 hour and 2 hours after injection.)

	J. S. act. 58. Rabbit I. 106 mg. %.	Non-diabetic male, act. 54. Rabbit II. 100 mg. %.
Fasting.	86	74
1/4 hour	66	76
1 hour	66	76
2 hours	48	66

Summary. This case represents an extreme degree of insulin resistance, in a patient whose diabetes mellitus was in other respects unremarkable. As high as 3250 units were given in 24 hours. Our experience in the critical period of coma indicates that very large doses of insulin may be required to save the life of the exceptional case. Further research is being undertaken with this patient in an attempt to uncover the fundamental factors underlying his insulin resistance.*

* The patient on July 26, 1938, is clinically well, the insulin dosage having been reduced to 440 units daily. On July 20 the 11-A.M. blood sugar was 138 mg. % and the urine at that time contained 1.8% glucose (glucose excretion about 15 gm. daily). Further evidence of the absence of a diabetogenic hormone of anterior pituitary origin has very kindly been furnished by Prof. C. N. H. Long, of Yale (June, 1938), who injected precipitates from the patient's blood and urine over 3 days to partially depancreatized rats known to be susceptible to anterior pituitary extract, with no effect on the glycosuria of these animals.

HYPERINSULINISM AND PREGNANCY.

REPORT OF A CASE.

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A CAREFUL search of the literature fails to reveal a single reported case of coëxisting hyperinsulinism and pregnancy, though 2 somewhat similar cases have been recorded. Schwarz¹⁸ reported a case of hypoglycemia in pregnancy, but in his patient there was an associated hyperthyroidism and the hypoglycemia occurred late in gestation. John¹³ reports a case of hyperinsulinism, successfully treated with insulin, in which, 2 years after recovery, normal pregnancy with delivery of a normal child occurred. No other reports of children born of hypoglycemic or hyperinsulinic mothers appear to have been made. The following case, therefore, is of special interest and should be on record.

Case Report. L. H., a white female, was married in 1920 at the age of 20. In 1921, labor was induced during the 8th month of her first pregnancy because of nephritic toxemia. In 1923, her husband's suicide precipitated a serious emotional disturbance which continued during the next 2 years.

In 1925, the patient married a brother of her first husband. In March, 1926, her second pregnancy ended spontaneously at 3½ months. In December, 1926, her third pregnancy terminated spontaneously at 3½ months with profuse hemorrhage.

In 1930, menstruation, which hitherto had been normal, recurring every 28 days and lasting 6 days, rapidly decreased to a flow of ½ to 1½ days. In 1931, the patient first came to me for treatment complaining of continual nervousness, with exacerbations consisting of irritability, weeping and depression. Examination was totally negative except that the patient appeared undernourished. Her weight was 93 pounds (42 kilo.) and her height 62 inches (157 cm.).

During the winter of 1931-32 there were numerous menstrual delays of from 6 weeks to 2 months. In 1932, there appeared occasional severe attacks of nausea and vomiting, each lasting 2 to 3 days, together with marked anorexia that persisted thereafter. During 1933, the menstrual irregularity and unrelated attacks of nausea and vomiting continued. For

about a month, beginning in May, 1934, the patient had recurrent evening fever, the temperature rising to between 99.5 and 100.5° F. and being irregularly associated with dyspnea, palpitation, nausea and fatigue. The patient was exhaustively studied at this time with totally negative results.

In October, 1934, she developed griping pain in the epigastrium, occurring shortly after arising in the morning and persisting for about 1 hour. This was followed by soreness at the site of the pain, belching and nausea. Examination revealed only epigastric tenderness. Attacks began to appear in the late afternoon, associated with fatigue, vertigo and faintness. They also occurred during the night, but less frequently. When I saw the patient in a severe attack one morning in November, 1934, she presented a picture strongly resembling that of overdosage of insulin. There was marked pallor, a cold clammy sweat, the pupils were widely dilated, and there were generalized tremors and facial twitchings. Speech was thick and somewhat unintelligible. The patient complained of severe epigastric pain, vertigo, and diplopia. These symptoms abated promptly when the patient was given sugar and orange juice. A glucose tolerance test done during the next week showed a flat curve (Chart 1). This was interpreted as being

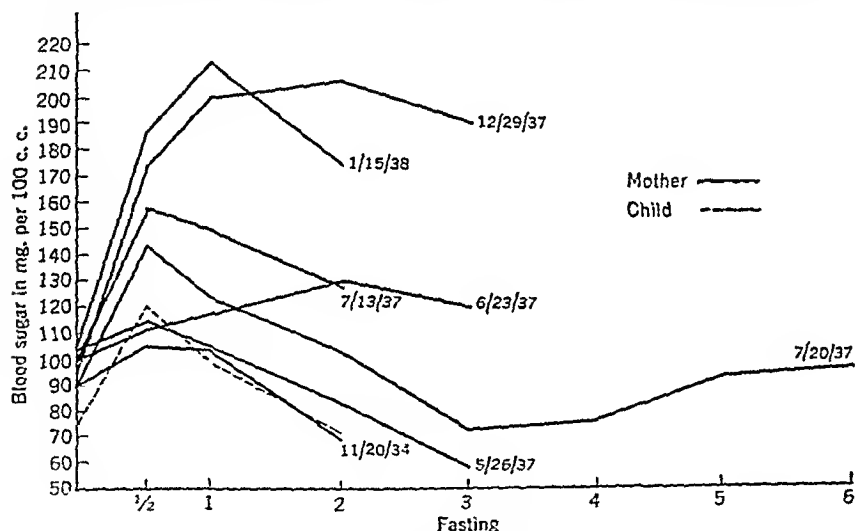


CHART 1.—Glucose tolerance tests on mother and child.

indicative of hyperinsulinism, although none of the specimens showed a marked hypoglycemia. When the patient began to take small amounts of food regularly between meals and on retiring, recurrence of her hypoglycemic symptoms were largely avoided.

During the first 5 months of 1935 the hypoglycemic attacks were under fair control. The menstrual irregularity became marked by increasingly frequent intervals of amenorrhea and progressively diminishing amount of flow, the catamenia now lasting only one-half day. Mental depression increased steadily. From June, 1935, she gradually became addicted to alcohol until she was taking as much as 16 to 20 ounces of whiskey in the course of an evening. In December, 1935, epigastric pain and vomiting reappeared. Several months of treatment with diet, psychotherapy and large doses of anterior pituitary-like sex hormone failed to bring about any improvement. In September, 1936, her tolerance for alcohol diminished rapidly and there was an increasing maniacal tendency, evidenced by fits of inexplicable rage

and unmanageability. Otherwise, the patient continued quite depressed, had persistent nausea and vomiting, marked anorexia and insomnia. Insulin therapy, as suggested by John,¹³ had to be promptly abandoned because as little as 5 units produced marked shock.

Early in November, 1936, nausea and vomiting became more pronounced. Because the patient had menstruated last on September 25, 1936, an Aschheim-Zondek test was done and proved positive for pregnancy. Announcement of this fact proved of great benefit to the patient, bringing about a prompt decrease in her symptoms. Vomiting persisted until the 10th week, insomnia and nausea until the 16th week when the patient was restored to a full diet with carbohydrate feedings between meals because of marked afternoon fatigue. In the 29th week (April 19, 1937) nausea and faintness began to occur at 3 A.M., waking the patient. Orange juice and sugar relieved these symptoms which subsided during the final 3 weeks of the pregnancy. A 3 A.M. specimen and 1 at 4 P.M. taken during the 34th week showed 67 mg. and 87 mg. of sugar per 100 cc. of blood respectively. A glucose tolerance test on May 26, 1937, showed a flat curve; another on June 23, 1937, revealed a moderate decrease in tolerance. Blood pressure and urine remained normal throughout the pregnancy. The weight gain was interesting. By the 27th week (Apr. 10, 1937) it had reached 118½ pounds and it remained at this level, about 24 pounds above the patient's usual weight, until term. After the 27th week, while the abdomen continued to enlarge, the patient definitely lost flesh about the face and extremities.

The fetus, which was first felt at 19 weeks (Feb. 2, 1937), was unusually active. Pregnancy ended on July 4, 1937, at full term. During labor, which lasted 7 hours, hypoglycemic symptoms occurred twice. The child was born spontaneously on July 4, 1937. The mother's blood sugar examined immediately after the end of the second stage of labor showed 107 mg. per 100 cc.

The puerperium was uneventful. Marked hypoglycemic symptoms which occurred during the first 3 days ceased after the patient was placed on a high fat-low carbohydrate diet¹³ made up of 60 gm. of protein, 90 gm. of carbohydrate and 180 gm. of fat. On this diet the patient gained weight. A glucose tolerance test on July 13, 1937, showed a definite decrease in tolerance; another on July 20 showed a slight increase.

The patient menstruated for the first time postpartum on Sept. 25, 1937, and again on Oct. 22, 1937, both periods being of 7 days' duration and of good volume. She felt and acted normally in all respects. In early November there was a recurrence of nausea, severe headache and backache, anorexia, insomnia and mental depression. There have been no further symptoms of hypoglycemia. Menstruation in November and December, 1937, was delayed, brief, and scanty. Glucose tolerance was found to be markedly reduced. Institution of insulin therapy (5 units 3 times daily) has resulted in marked remission of all symptoms with tendency to only very mild insulin reactions.

Insulin therapy was begun on January 17, 1938. The first subsequent menstruation occurred January 28 to 31, with a freer flow than in November and December, 1937. Menstruation in February to May, 1938, inclusive, has in each instance been of 3 to 4 days' duration, of normal volume, and only slightly delayed.

The patient has had mild acne rosacea for about 15 years. This condition improved very greatly during the last pregnancy but recurred in severe form in November, 1937, with the return of menstrual and mental symptoms. On institution of insulin therapy the acne improved almost to the point of total disappearance and has since shown mild exacerbations only immediately preceding menstruation. This observation is in accord

with that of Wortis²¹ in the insulin hypoglycemia treatment of dementia præcox patients who also had acne vulgaris.

The child, a normal female, weighed 6 pounds and 2 ounces at birth. Her venous blood sugar 72 hours after birth was 71 mg. per 100 cc. of blood. There has been no symptomatic evidence of hyperglycemia or hypoglycemia. Several urine specimens have been negative for sugar. At the time of this report development, including dentition, nutrition, mentality and growth, has been normal. Repeated glucose tolerance studies have shown the normally flat curve characteristic of infants (Chart 1).

Discussion.—The etiologic considerations in this case are as important as they are interesting. The comparatively mild symptoms would place this patient in the group of relative or secondary hyperinsulinism. The primary endocrine dysfunction appears to be in the pituitary gland. While Simmonds' disease presents itself for consideration, most of the characteristic features of pituitary cachexia are not evident in this case. The so-called functional cases of chronic hypoglycemia tend to display a flat glucose tolerance curve.¹ The present case repeatedly showed such curves.

The existence of such an entity as hyperinsulinism was postulated by drawing a parallel between the pancreas and the thyroid gland.^{2,11,19} Psychic trauma, a possible etiologic factor in exophthalmic goiter, might reasonably also be a factor in relative hyperinsulinism. A violent psychic disturbance occurred in my patient and its rôle, directly or indirectly, in the etiology of the disturbance of insular function is at least probable. The mechanism of the influence of psychic trauma in hyperthyroidism and hyperinsulinism is uncertain. Experimental studies indicate that the higher nervous centers take part in the regulation of insular secretion through the vagus.^{3,22a} Disturbances in function may take place through the mediation of other glands. There is experimental evidence that the pituitary gland acts on the pancreas to increase insulin output both directly and through the thyroid gland.^{22b} Prolonged perversion of function may conceivably induce organic changes in the form of hypertrophy and hyperplasia. It is possible that the more severe cases of hyperinsulinism associated with hyperplastic and hypertrophic changes in the Islands of Langerhans (but excluding tumors of the islands) represent the ultimate result of perversion of function caused by endocrine disturbances in other glands. This would account for earlier or milder cases of hyperinsulinism without demonstrable pancreatic disease. It would explain also the failure of partial resection of the pancreas to abolish symptoms of hyperinsulinism in some cases.

The menstrual disturbances in the present case were related to and probably secondary to the hyperinsulinism. There is ample proof that irregularities in insulin secretion produce similar irregularities in menstruation.^{4,5,14,20}

Reports indicate an increased functional activity of the Islands of Langerhans during pregnancy, particularly during the middle period

and toward the end of gestation, followed by gradual decrease just before parturition.^{8,17} In the present case, hypoglycemic symptoms were more marked between the twenty-ninth and thirty-seventh weeks of pregnancy. The glucose tolerance studies show that tolerance began to decrease in the final weeks of pregnancy and continued to decrease after parturition. An attempt made to increase the glucose tolerance by restoring the patient to a high carbohydrate

TABLE 1.—GLUCOSE TOLERANCE TESTS ON MOTHER AND CHILD.

Time.	Mother.							Child.		
	11/20/34.	5/26/37.	6/23/37.	7/13/37.	7/20/37.	12/20/37.	1/15/38.	1/12/38.	2/2/38.	2/21/38.
Fast	92	104	100	100	91	96	107	80	77	76
$\frac{1}{2}$ hr.	105	115	112	158	143	176	188	116	120	117
1 hr.	104	104	118	150	125	200	214	80	100	93
2 hr.	70	84	130	128	103	206	176	72	71	82
3 hr.	...	57	121	...	73	192	.			
4 hr.	77					
5 hr.	94					
6 hr.	96					

All urine specimens in all tests were negative for sugar; 1.75 gm. glucose per kilo in all tolerance tests.

diet for 1 week preceding the final curve^{12a,b} seemed to have only slight effect. One may conclude that pregnancy favorably influenced the hyperinsulinism in this case. The reasons for this improvement are uncertain. They may depend on the widespread alteration in function of all the endocrine glands, ordinarily present in normal pregnancy, with secondary changes in pancreatic function. They may depend on insulin relationship between fetus and mother. Increasingly numerous reports of children with hyperinsulinism born of diabetic mothers,^{6,7,9,10} as well as reports of children with thyroid enlargement born of hypothyroid mothers¹⁶ and of cretins born of mothers with exophthalmic goiter^{15,16} point strongly to an interchange of endocrine substances between fetus and mother. A transfer of insulin from fetus to mother would depress maternal pancreatic function. Experimental and clinical evidence indicates that injections of insulin reduce activity of the Islands of Langerhans.^{13,21c} In the present case fetal insulin may have been the equivalent of injected insulin in depressing maternal pancreatic islet function. The improvement of the hyperinsulinism in this case, if due to general maternal endocrine changes of pregnancy or to fetal influences, would obviously be temporary.

The endocrine relationship between fetus and mother as cited above has in no demonstrable manner affected the child in this case. There is no evidence of diabetes or hyperinsulinism in the child. To date development has been normal in all respects.

Summary.—1. A case of hyperinsulinism and pregnancy with successful delivery is herein reported.

2. The pregnancy appears to have lessened the hyperinsulinism in the mother, reducing the sugar tolerance.

3. The child is normal in all respects.

4. The possible etiology of the hyperinsulinism in this case is discussed. In addition to accepted causes, psychic trauma, as noted in this case, appears to be a probable cause.

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UVEO-PAROTID FEVER (HEERFORDT'S SYNDROME) NEUROLOGIC MANIFESTATIONS.

REPORT OF TWO CASES.

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UVEO-PAROTID fever is either rarely encountered in the practice of most physicians or else the syndrome is mistakenly diagnosed as some other disease. Most standard textbooks on medicine fail to make any mention of this condition, yet the similarity in cases thus far reported unquestionably justifies its classification as a separate clinical entity. Uveo-parotid fever may be defined as a comparatively rare affection, characterized by inflammatory lesions of the uveal tract, a bilateral almost painless enlargement of the parotid glands, a low grade chronic fever, subject to many variations and by the occurrence of irregular constitutional symptoms. Paralysis of cerebrospinal nerves, particularly the facial nerves, occurs frequently. The majority of the patients have been in the second and third decades of life, although it may occur at any age. It is somewhat more prevalent in females, of the white race, though several cases among negroes have been recorded.

Uveo-parotid fever, as a clinical syndrome, was first recognized and described by the ophthalmologist Heerfordt,¹¹ of Copenhagen, in 1909. Under the name "Febris uveo parotidea subchronica," he reported 3 cases and discussed 2 others with similar clinical features, and expressed the belief that this disease was an atypical form of mumps. Merrill and Oaks¹⁹ reviewed the literature up to 1931, and Garland and Thomson,⁹ in a very comprehensive study, summarized 47 cases from the literature in 1933. More recently, Levin¹⁵ analyzed 66 cases, from the neurologic standpoint.

Case Reports. CASE 1.—Patient M.D. (Fig. 1), a 22-year-old negro housewife, was admitted to this hospital on November 3, 1937, complaining



FIG. 1.—Case 1. Three weeks after admission, shows some enlargement of the parotid glands and ptosis of the eyelids. Note the skin eruption on the face.

of fatigue, lassitude and malaise of 5 months' duration, drooping of the eyelids, and swellings at the angles of the jaws. The swelling of the left side of the face was present for 6 weeks and that on the right for 3 weeks. At the onset of her illness, she complained of a slight pain in the left side of the face. She had been nearsighted for many years, but spots appeared before her eyes and she was unable to see distinctly for 3 weeks prior to her admission. She was drowsy and very thirsty, drinking up to a gallon of water daily. Rinsing the mouth with water did not relieve her thirst. She lost 8 pounds in weight within 3 months. There was no history of skin eruptions and her menses were regular. Her past history revealed that at the age of 14 years, she was confined for 8 months to an institution, because of an incipient tuberculosis. The family history disclosed tuberculosis as the cause of death of both her mother and father. She has 3 brothers and 1 sister, but has no knowledge of their whereabouts or health. She has 3 healthy children.

General Medical Examination. The patient was an intelligent, young colored female and not acutely ill. Several small, shotty glands were palpable in the cervical region. Both parotid glands were enlarged, the left somewhat more so than the right. The enlargement was diffuse and more marked over the preauricular portions. The other salivary glands as well as the lachrymal glands were not enlarged. Stenson's ducts were not pouting or inflamed. The other findings were essentially negative. The blood pressure was 110/84. Neurologic examination: The gait and station were not tested because she was in bed with a temperature of 101° F. The pupils were in mid-dilatation, equal and reacted promptly to light and in accommodation. The left pupil was slightly irregular and there was some difficulty in convergence in the right eye. Leukomata were noted on both corneas, and the anterior chambers were distinctly deepened. The fundi oculi and perimetric visual fields were within normal limits, but her visual acuity was considerably reduced (20/200). Ocular tension, O.D., 18; O.S., 20. Bilateral ptosis of the eyelids with a tendency to chronic wrinkling of the forehead were noted. The other cranial nerves, grossly tested, were intact. The upper deep reflexes were present and equally active. The right knee jerk was more active than the left. The abdominal reflexes were present and equal. On plantar stimulation there was a prompt flexor response on the right, but none on the left. Sensory examination was normal to all modalities.

Laboratory Findings. Urine: Specific gravity, 1006 (on 2 concentration tests). No abnormal constituents were found. The daily fluid intake in ounces ranged from 147 to 196 and the output from 192 to 129. Pituirrin given intramuscularly reduced the intake and output by about 50% but had to be discontinued after 3 days because of the complaint of severe headache. Blood: Hemoglobin, 70; leukocytes, 11,200; neutrophils, 68; lymphocytes, 32; erythrocytes, 3,800,000. Chemistry (in mg. per 100 cc. of blood): Sugar, 120; urea nitrogen, 14; creatinine, 1; total protein, 8%; albumin, 5%; globulin, 2.6%. Wassermann test, negative. Spinal fluid: initial pressure 150 mm. of water, clear, colorless, no cells, total protein 0.22 mg. %, No evidence of block. Wassermann and colloidal gold tests were negative. Mantoux tuberculin test was negative. Basal metabolism was -18. An aspiration of the parotid gland was attempted but insufficient material was obtained for microscopic study. A biopsy of the parotid was refused. Electrocardiographic tracings showed a depressed *T* wave in Lead II and an inverted and coved *T* wave in Lead III, suggestive of cardiac involvement. Roentgen ray studies were made at various intervals and reported by Dr. Samuel Weitzner. A chest plate taken on Dec. 30, 1936 (Fig. 2), showed no abnormality. On Nov. 5, 1937, another film (Fig. 3) disclosed a distinct and marked enlargement of the glands at both lung roots. On Nov. 30, 1937, a radiograph of the chest revealed a marked enlargement of the glands at both lung roots and scattered throughout both lungs were small, punctate areas of infiltration, but no evidence of pleural effusion (Fig. 4). Roentgen rays of the mandible and supramandibular regions showed no evidence of calculi in the salivary glands. Roentgenograms of the skull, including the sella turcica, and of the long bones were negative.

Course. During her stay in the hospital the swelling of the parotid glands gradually diminished and upon her discharge on Dec. 14, 1937, there was practically no enlargement visible or palpable. No change was noted in the eyes, but the bilateral ptosis had improved considerably. It is interesting to note that the water intake and output was diminished for several days following the injections of pituitrin. This began with the third injection and continued for 3 days after the medication had been discontinued. The temperature was within normal range during most of her stay.

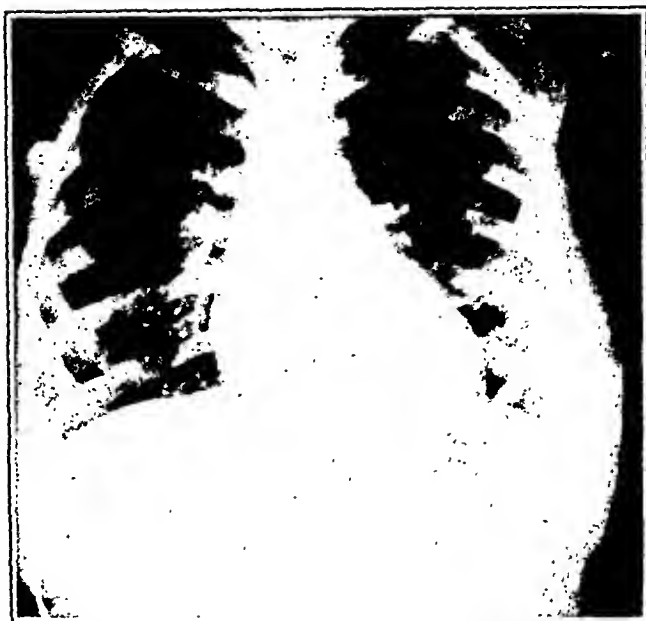


FIG. 2.—Case 1. Roentgen ray of the chest shows no enlarged glands at the lung root.

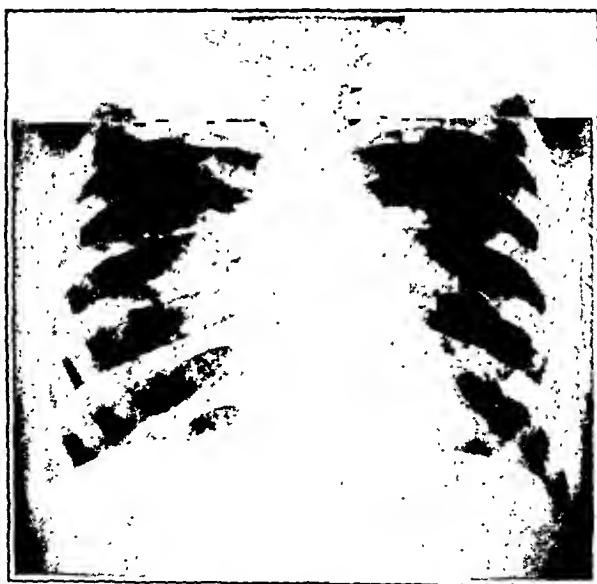


FIG. 3.—Case 1. Two days after admission Roentgen ray of the chest discloses a marked enlargement of the glands at both lung roots. The glands are fairly sharply circumscribed.



FIG. 4.—Case 1.—Film taken 25 days later reveals that the glands are somewhat larger. No other change is noted.

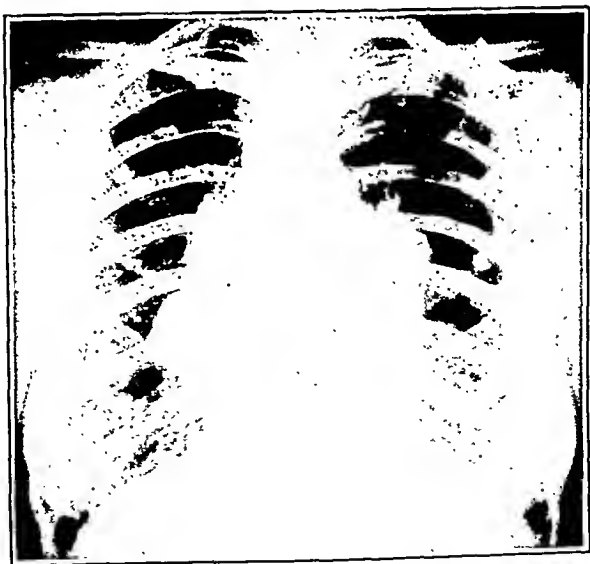


FIG. 5.—Case 2. Roentgen ray of the chest is essentially negative except for bilateral enlargement of the glands at the lung roots. Note the discreteness of these glands. Another film taken one month later, showed no appreciable change, despite adequate radiotherapy.

On discharge, she merely complained of a slight numbness of the face, but the facial weakness was much less apparent. Despite the recession in most of the clinical findings the Roentgen rays of the chest showed progressive changes in the lungs and mediastinum.

CASE 2.—A. S., a white married female aged 34, was admitted to this hospital on July 25, 1937, with the complaints of progressive weakness, night sweats, loss of 30 pounds of weight, excessive thirst and frequency of urination, of 6 months' duration. She had been having a low-grade fever running up to 102° F. in the evenings, for 6 weeks prior to her admission. A swelling at the angles of both jaws had been present for about the same period of time. Amenorrhea of 3 months' duration and persistent blurred vision during the same interval were elicited in the history. She had one child and no other pregnancies. The family history, as far as any related condition was concerned, was essentially negative, and irrelevant. Her past history was also negative.

Medical examination revealed a chronically ill female of about 34, well developed and fairly well nourished. A diffuse purulent postnasal drip was seen. The tonsils were markedly enlarged and cryptic. The trachea was in the midline and freely movable. There was a slight increase of retro-manubrial dullness to the right and left. A low pitched systolic murmur was heard at the aortic and apical regions, somewhat louder at the former area. On percussion, liver dullness extended to about 3 fingers below the costal margin. The spleen was barely palpable. Several small lymphatic glands were felt in the inguinal regions. Both parotid glands were slightly enlarged but not tender to pressure. Old pigmented areas were noted over both tibiae, as well as telangiectasiae over the upper part of the chest wall anteriorly. Blood pressure was 120/70.

Neurologic examination revealed that her visual acuity was markedly reduced. The pupils were both irregular and reacted sluggishly to light and in accommodation. Bilateral uveitis, posterior synechia, ciliary injection, deposits on Descemet's membrane and increased relucency of the anterior chamber were noted. Because of the opacities, the fundi oculi were not visualized. There were no extraocular muscle palsies. All the other cranial nerves, grossly tested, were intact. The biceps, triceps and the knee jerks were markedly hyperactive and equally so on both sides. The ankle jerks were present and somewhat diminished. There was no muscle or nerve tenderness. An equivocal Babinski was elicited on the right. Sensation was normal to all modalities.

Laboratory Findings. Urine: Specific gravity 1010 to 1012 with a faint trace of albumin, occasional white cells and coarse granular casts. Blood: Wassermann test, negative. Chemistry in mg. per 100 cc. of blood: Sugar, 95; urea nitrogen, 16; uric acid, 1.6; creatinine, 1; cholesterol, 580; ester, 415; total protein, 6.8%; albumin, 2.2%; globulin, 4.6%; hemoglobin, 84%; white blood cells, 6400; segmented polys, 41; non-segmented polys, 40; lymphocytes, 10; monocytes, 7; eosinophil, 1; basophil, 1.

Electrocardiographic tracings showed a sinus tachycardia, tendency to left ventricular preponderance, and low T waves suggestive of involvement of the ventricular musculature. Roentgen ray films of the knees, lumbosacral spine and both shoulders showed no abnormalities of the bones. Roentgenographic film of the chest on June 26, 1937 (Fig. 5), showed a group of moderately enlarged masses at both lung roots. The appearance was that of enlarged glands bilaterally. On July 22, 1937, another plate disclosed no appreciable diminution in the size of the enlarged glands in both lung roots and the findings were practically the same as on the first examination.

Course. The patient received a series of deep Roentgen ray treatments to the mediastinum and to the parotid gland regions. The glandular

enlargement promptly receded during the treatment but the mediastinal glands were not altered. She had fever daily, ranging about 101° F., never reaching the normal level. When biopsy of the parotid glands was suggested the patient signed herself out of the hospital, against advice. She was admitted to the Mount Sinai Hospital on Sept. 23, 1937, and they reported that a biopsy of the tonsils showed fragments of hyperplastic tissue and one epithelioid cell tubercle. Because of an increasing tension in the left eyeball, an iridectomy was performed. The specimen removed was reported as showing fragments of iris with several epithelioid cell tubercles. The patient ran a completely afebrile course during her 6-week stay and there was no change in either the visual disturbances or the evidence of mediastinal lymphadenopathy. At Mount Sinai Hospital the differential diagnosis lay between uveo-parotid tuberculosis and Boeck's sarcoid.

Etiology. Many different etiologic factors have been proposed as the cause of this condition, but the majority of clinicians and pathologists are now of the opinion that tuberculosis is the primary factor. Briefly and for purposes of clarity we have divided the opinions into two groups:

I. Those Favoring Tuberculosis as a Primary Etiologic Factor. Lehmann¹⁴ stated that the condition might be due to an atypical form of tuberculosis. Souter²⁷ expressed the belief that tuberculosis is the cause and stated, "The mechanism that may be assumed is that absorption from tuberculous bronchial or even mesenteric glands causes the parotitis and uveitis and that in the worst varieties of iridocyclitis actual bacilli possibly of a non-virulent type, as suggested by Wilmer, may reach the eye." Search for the tubercle bacillus was unsuccessful until Souter²⁷ and Tanner and McCurry²⁹ found it in the lesions. McCurry actually demonstrated the tubercle bacilli in biopsy sections from both parotid glands of a patient suffering from this malady.

Garland and Thomson⁹ declared that "In no case in which a biopsy was performed was histologic evidence of tuberculosis lacking," and that they had found incontrovertible evidence of tuberculous infection in more than one-third of 21 recorded cases. Cavara⁴ injected material (obtained from biopsies on the lachrymal and parotid glands) intraperitoneally into 3 guinea pigs, with negative results in 2, but produced fatal generalized tuberculosis in 1 which, on autopsy, showed considerable caseation at the site of the injection and in the regional lymph nodes. He concluded that uveo-parotid fever is due to a special type of tuberculosis. Muller²² reported the case of a boy from whom a biopsy of the parotid gland showed an endothelioid type of tuberculosis, and who presented nodules in the iris morphologically resembling those seen in tuberculosis. McCulloch,¹⁷ on slit lamp examination, noted tubercles along the periphery of both irides in a case reported by him. At times, collateral evidence of tuberculosis is indicated by the family history, clinical signs such as night sweats, lassitude and loss of weight, pleural effusion, cervical adenitis, favorable reaction to tuberculin and roentgenograms.

II. *Those Opposed to the Concept of a Tuberculous Origin.* Authors whose particular cases revealed no clinical features indicative of tuberculosis are mainly in this group. Heerfordt¹¹ and Lecksmas¹³ believed that uveo-parotid fever was an atypical form of mumps. Fuchs⁷ and others^{3,10} were of the opinion that this condition was very closely allied to Mikulicz' syndrome. It was classed as a deficiency disease by Ramsay.²⁴ Mohr²¹ ascribed the lesions to syphilis, because of positive serologic evidence in his case. Infections of the mouth^{1,18} and generalized toxemia⁶ were also considered as possible causes. Merrill and Oaks¹⁹ attributed this disease to a "specific virus or bacterium as yet undetermined." Because animal inoculation gave negative results, Weve³⁰ believed that this malady is not truly of tuberculous origin and that it might be a tissue response to an unknown infectious agent allied to tuberculosis and designated it as "paratuberculosis." Parker²³ stated that the "weight of evidence both from the clinical course and the reported cases suggests very strongly that the condition is rheumatic in nature and thus its protean manifestations." That the disease is "an infective allergic condition caused by an organism as yet not isolated, which produces a low grade infection in a sensitized individual" was indicated by Cohen and Rabinowitz,⁵ while others¹⁶ are of the opinion that the disease is an allergic reaction to many allergens, one of which may be tuberculosis.

Many competent investigators are opposed to the theory of tuberculosis as the cause of the condition because the results of animal inoculations and tuberculin tests are more often negative than positive, and because, from a clinical point of view, these patients seldom show objective symptoms and signs of tuberculous infection.

Symptomatology. While there seems to be great variation in the order of appearance, severity and duration of the symptoms, they may be considered under:

1. *Prodromata* are frequently, though not constantly, elicited in the anamneses, and may be present from a few days to several months. They include general malaise, weakness, lassitude, drowsiness, anorexia, gastro-intestinal upsets, loss of weight, puffiness of the eyelids, long continued dryness of the mouth, dysphagia, cough, night sweats, pains in the chest, abdomen or joint paresthesias, polyuria without glycosuria and paralysis of other cranial nerves besides the facial. A chronic, low grade fever is common but is not a constant finding. The temperature may range from the slightest elevation to 103° F., in some instances. An afternoon rise is common.

2. *Glandular* enlargement of the parotid glands is a constant finding. It is generally bilateral, but occasionally is unilateral. The glands may be hard or nodular, not adherent to the skin, and while painless, as a rule, may be tender to pressure especially at the onset of the disease. The swelling may be limited to the preauricular

area or be more extensive and involve all of the parotid gland. The enlargement is usually of several weeks' duration but may last for months and even years. The swellings may recur but are usually of a chronic type and resolve without suppuration. In addition to the parotid enlargement, submaxillary, sublingual and lachrymal swelling may occur in the same individual at the same time. Among the lymphadenopathies, cervical gland enlargement is most and bronchial gland is least commonly involved. Hilar gland involvement was also reported.^{16,29}

3. *Ocular manifestations* though quite variable are present in all cases and are probably the most important of the diagnostic symptoms in this syndrome. The ocular disturbances may come on suddenly or insidiously and may persist for a week or for years. As a rule, the glandular swellings are the first signs, but in some cases, ocular difficulties, both subjective and objective, either precede or are concomitant with the glandular enlargement. The most prominent eye findings are uveitis with predominance of iritis and cyclitis. It is often the earliest symptom and the resulting visual impairment may be permanent. The onset may be unilateral with pain and dimness of vision or, as invariably occurs, the uveitis may be bilateral and of a nodular type. Other ophthalmologic conditions such as corneal herpes, vitreous hemorrhages and opacities, keratitis, optic neuritis or atrophy, neuroretinitis, choreoretinitis, aqueous turbidities, conjunctivitis, glaucoma and cataract may occur. They may also include mistiness or dimness of vision with more or less impairment of sight, narrowing of the palpebral fissures and ciliary congestion. The pupils may be dilated, irregular and fixed to light and in accommodation. There may be posterior synechiæ or one may note fatty deposits in the posterior surface of the cornea and the anterior surface of the lens. Nodules, definitely identified as tuberculous, are said to occur in the iris of these patients.

4. *Neurologic complications* have received comparatively little attention as they are overshadowed by the parotid and ocular manifestations. Levin¹⁵ expressed the opinion that 50% of the cases present some abnormality of the nervous system. Neural involvement shows great variability and may range from cranial to peripheral nerve affections.

Facial palsy, usually of the peripheral type and of varying degrees of intensity and duration, is the commonest neurologic complication. It may be bilateral although it more frequently is unilateral. Whether the palsy results from pressure on the nerve by the swollen gland is still a moot and unsettled question. As a rule, the facial nerve involvement, when it occurs, follows the parotitis in from a few days to 6 months, but in several instances it has preceded the parotitis by varying lengths of time and in other cases the facial impairment occurred simultaneously with the parotitis. Because

the paralysis is often limited to the lower part of the face, Garland and Thomson⁹ explained the peripheral facial palsy on the basis of pressure by the parotid gland on the nerve as it leaves the stylo-mastoid foramen, whereas there was evidence (involvement of taste in the anterior two-thirds of the tongue) in Mohn's²⁰ case to place the site of the lesion somewhere between the geniculate ganglion and the branching of the chorda tympani (in the bone itself) thus excluding pressure from the parotid gland, which, incidentally, was not yet enlarged. Facial palsy developing when the parotitis is subsiding is probably due to the cirrhotic nature of the inflammatory lesion.⁹ Altland-Duisburg² thought that the facial paralysis is due to a toxin analogous to that producing the paralysis in the late stages of diphtheria and that it indicated rather a particular causative agent. Tait²⁸ believed that the neuritic manifestations may be due to a circulating toxin.

Among the other cranial nerve impairments, diplopia and strabismus are rare. Partial ptosis of the eyelids, unilateral or bilateral, is not uncommon. In both of our cases ptosis was a prominent presenting sign. Pupillary changes secondary to the uveitis are fairly common. Involvement of the sensory portion of the trigeminal nerve was mentioned,¹⁵ but the motor portion, as far as we could find, was not involved in any of the cases thus far reported. Nerve deafness of the central type is occasionally encountered.^{9,20,27} Dysphagia is fairly common and has been considered to be evidence of cranial nerve paralysis by many investigators, but others⁹ thought it was due to the lack of salivary secretion resulting from the parotitis. Vocal cord paralysis^{11,28} and paralysis of the soft palate²⁴ are rarer findings. Dysarthria is occasionally a prominent symptom²⁷ and has been attributed both to dryness of the mouth and to muscular weakness following the facial palsy. Loss of the sense of taste, disturbance of the innervation of the uvula and hypesthesia of one side of the tongue⁵ are very rare. Hallucinations and meningeal signs have been noted. Delirium and convulsive seizures occurred in 1 case, and at autopsy, multiple tuberculomas were found.³ Hypersomnia is not uncommon.

Involvement of the spinal nerves may be manifested by a diminished tactile, pain and temperature sense, reduction or abolition of the deep tendon reflexes, tenderness over the peripheral nerves, paresthesias, and wrist or foot drop. The knee jerks may be markedly diminished or absent,⁹ the ankle jerks may not be elicited, or all the deep tendon reflexes may be depressed or abolished.^{9,20,27} Intermittent claudication, paralysis of the extremities, with definite pyramidal tract involvement have been reported.³

5. *Other Manifestations.* A. *Polydypsia and polyuria* associated with a dilute but otherwise essentially normal urine have been noted. Levin¹⁶ believed that these symptoms represented a true diabetes insipidus.

B. *Skin lesions*: early in the illness, there is not infrequently a patchy, non-elevated erythematous rash, without itching and involving particularly the extensor surfaces of the arms and legs. The rash is generally of short duration. Other skin eruptions include erythema nodosum,^{19,24} xerodermia of both legs,⁸ papulo-necrotic tuberculosis,²⁵ urticaria, and petechiæ.¹²

C. *Joint pains and polyarthritis* have also been reported.^{19,27}

D. *Amenorrhea* is not an infrequent finding,^{8,26} and was present in Case 2.

Laboratory Findings. 1. *Urine* is generally negative, except for a low specific gravity when there is an altered water metabolism.

2. *Blood*, as a rule, reveals no definite abnormalities except for an occasional secondary anemia. In some instances, eosinophilia has been noted.

3. *Spinal fluid* may reveal a moderate pleocytosis (5 to 20 lymphocytes) or a slight increase in protein content or both.

4. *Wassermann tests* are generally negative both in the blood and spinal fluid.

5. *Tuberculin test* is more often negative than positive.

6. *Electrocardiograms* in some cases are abnormal, suggestive of myocardial involvement.

7. *Roentgen rays* of the chest, in many cases, sooner or later disclose varying extents of pulmonary lesions, especially enlargement of the glands at the lung roots. Roentgen rays of the skull and long bones have not revealed any gross defect.

Differential Diagnosis. 1. *From Mumps*. The fact that many of the patients had mumps in childhood, and that at the time they had uveo-parotid fever, they had not been exposed to mumps, the long prodromal period, the chronic nature of the condition, the frequent bilateral facial palsy, which may antedate the parotitis, the absence of orchitis, and further, that individuals in contact with these patients did not develop a similar condition, should conclusively eliminate mumps in the differential diagnosis.

2. *From Syphilitic Parotitis*. In early syphilis the gland swells rapidly, is tender to touch and has a firm, tense, reddish surface. The swelling is usually bilateral but not symmetrical. Suppuration may occur in the neighboring lymph nodes. The mass is closely adherent to the underlying tissues. In late syphilis the parotitis develops insidiously. The tumor mass becomes attached to the underlying tissues and the skin. Fluctuation develops with the eventual appearance of a gummatous ulcer. Syphilis can be easily ruled out by history, examination and serologic findings.

3. *From Mikulicz' Disease*. This is a rare and still obscure malady, characterized by a chronic swelling of the salivary glands, particularly the parotids, but also involving the submaxillary and sublingual glands and occasionally the lachrymal glands. The patients frequently develop tuberculosis later. Here, ocular mani-

festations seldom occur. Mikulicz' disease in many ways seems to be allied to uveo-parotid fever, and, at times, a group of cases of one disease probably contains instances of the other.

4. *From Boeck's Sarcoid.* This condition should be considered where lesions suggestive of tuberculosis are found but no caseation or tubercle bacilli can be demonstrated. However, Boeck's sarcoid differs somewhat from uveo-parotid fever in several ways. In the former disease, there are characteristic skin manifestations which may assume one of three forms, *i. e.*, small disseminated nodules, infiltrations or large cutaneous nodosities. Roentgen rays of the hands and feet show a reticulum-like appearance in the small bones which may extend to the long bones. Pathologically, the lesions in both conditions may manifest the same features (a miliary epithelioid tubercle with occasional giant cells, but with almost complete absence of necrosis). Many authors are of the opinion that the two diseases are one and the same.

5. *From Encephalitis Lethargica.* That uveo-parotitis may simulate encephalitis has been commented upon by Levin. However, in obscure cases of encephalomyelitis or polyneuritis, especially when complicated by parotitis, the diagnosis of uveo-parotid fever must be borne in mind.

Prognosis and Treatment. The prognosis is good, and the mortality is estimated at about 5%. Death, in the rare instances in which it occurs, is due to miliary tuberculosis. The disease runs a chronic course, and one of its features seems to be the irregularity in the onset and progression of the symptoms. Regardless of the duration of the parotitis, its tendency is to improvement without suppuration, but it may recur. The ocular symptoms, however, may persist or even become permanent.

Some authors have advocated symptomatic treatment with tonics, such as inorganic arsenic, whereas others have employed thyroid extract, foreign protein, tuberculin and Roentgen ray therapy.

Summary and Conclusions. Our study indicates the comparative rarity of uveo-parotid fever even in a large general hospital. The condition is probably more common than is usually suspected, but is rare enough not to be readily discerned. To date, less than 100 cases have been reported and the majority have appeared in Scandinavian and German journals of ophthalmology. A review of the literature reveals a multiplicity of suggested etiologic factors among which are atypical mumps, syphilis, beri-beri, diphtheria, allergic reaction, toxemia, oral sepsis, virus, infection and pseudoleukemia. It has also been designated as a variety of Mikulicz' disease. Most of these theories have been abandoned and the problem now resolves itself into whether this clinical entity is due to tuberculosis or to some as yet undiscovered infectious agent such as a virus. There is considerable, though not altogether conclusive, evidence in support of the tuberculous theory. However, none of the theories

so far advanced has an unassailable foundation. Our knowledge of uveo-parotid fever will be materially aided if and when either the causative agent of Boeck's sarcoid is found or when there are many more unequivocal demonstrations of tubercle bacilli in the lesions. Until then, the assumption of a tuberculous basis seems plausible and probable, but that it may be a specific infection due to an unknown virus cannot with absolute certainty be excluded.

The symptoms are essentially a uveitis associated with a parotitis, with a low grade chronic fever. There are many prodromata. Neurologic complications are common. The disease is to be differentiated from mumps, syphilitic parotitis, Mikulicz' disease, Boeck's sarcoid and encephalitis lethargica. The prognosis is good as to life and fair as to residua.

We are indebted to the medical department for its coöperation and permission to publish these cases.

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REGENERATION OF THE ADRENAL GLAND FOLLOWING ENUCLEATION.

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WE have shown previously that when the adrenal glands are removed from their normal position and grafted elsewhere in the same animal, complete degeneration of the medulla and entire

cortex takes place, except for a narrow zone of glomerulosa and capsule. From these persistent tissues, however, a functional mass of cortical tissue rapidly regenerates, and in a few weeks a gland, without medulla, equal to or greater in size than the original gland, is restored. Likewise, we have shown that when the capsules, with a narrow zone of cortical cells adherent to them, are removed from the rest of the gland and grafted to the ovaries, a functional mass of cortical tissue will soon regenerate. However, when the central portions of the gland, including medulla and most of cortex but without the capsule, are grafted, then regeneration does not take place.

Enucleation is a method employed by physiologists to free the adrenal gland of all medullary tissue and yet secure an adequate amount of cortex to meet the functional requirements of the organism. Evans² in studies on the adrenal cortex and carbohydrate formation described this method of securing demedullated adrenal glands. Scant attention, however, has been paid to factors which control the extent of regeneration of cortical tissue after the medulla and most of the cortex of the gland have been removed.

This report is concerned with the regeneration of the enucleated adrenal gland as influenced by: 1, the presence or absence of one intact adrenal gland; 2, treatment with cortin; 3, removal of the pituitary body; and 4, age.

Methods. Rats of the Wistar strain were used in these experiments. Unless otherwise designated, male animals weighing 170 to 200 gm. were selected. Enucleation was carried out through a lumbar incision. The adrenal gland was located and carefully freed of its fat investment. Without damage to the blood supply the anterior tip of the gland was carefully excised and then, with fine forceps, the body of the gland, including all of the medulla and most of the cortex, was gently expressed. The remaining capsule and the narrow zone of glomerulosa adhering to it was then replaced and the peritoneum closed. Data collected on the weights of adrenal glands and on the amount of glandular material expressed from the capsule indicated that there was left after enucleation of the adrenal gland an amount of adrenal substance, including capsule, weighing approximately 3 mg.

Hypophysectomy was carried out employing the usual parapharyngeal approach. The glands were removed by negative pressure. When partial hypophysectomy was performed, the anterior lobe was divided into two halves by means of a fine needle. The one-half of the anterior lobe was removed with a fine pipet, exposing the posterior lobe which was similarly removed, thus leaving one-half of the anterior lobe intact.

Bilateral enucleation was always performed as a single stage operation. When unilateral enucleation was carried out, the left adrenal gland was always enucleated and the right adrenal gland was either left intact or removed completely from the body. In those animals which were hypophysectomized, bilateral enucleation of the adrenal glands was carried out at the same time. It was necessary to treat the hypophysectomized adrenal-enucleated animals with 1 cc. of cortin, which was given daily by subcutaneous injection. This amount is inadequate to inhibit regeneration of the adrenal glands of non-hypophysectomized rats.

The rats were maintained on a commercial diet containing 0.24 % sodium and 1 % potassium. The animals were killed by exsanguination. The

regenerating cortical masses were weighed by a standardized procedure and were to the nearest milligram. All adrenal tissue was fixed and stained with hematoxylin and eosin, and for the chromaffin reaction.

Procedures. Four individual experiments were carried out. In Experiment 1, 28 rats were closely matched on a basis of weight into 14 pairs. The left adrenal gland of each animal was enucleated. In 6 animals the right adrenal gland was removed from the body at the time of enucleation, and in the other animal of the pair the right adrenal gland was left intact. One pair of these animals was killed each week. In the case of the 8 remaining pairs of animals the right adrenal gland was removed from 1 animal of each pair 2 months after enucleation of the left adrenal. In the other animal of the pair the right adrenal gland was left intact. One pair of these animals was then killed at weekly intervals for 8 weeks.

In Experiment 2, the left adrenal gland was enucleated in 38 animals. All of these animals were closely matched on a basis of weight, and each animal was designated to an experimental group by chance selection. In a group of 12 of these 38 animals the right adrenal gland was removed. In a second group of 10 animals the right adrenal gland was left intact. In a third group of 6 animals the right adrenal gland was removed and the animals were given 2 cc. of cortin subcutaneously every 8 hours. In a fourth group of 10 animals the right adrenal gland was removed and the animals were given 5 cc. of cortin daily in their drinking water. All animals were killed for necropsy 21 days after operation.

In Experiment 3, bilateral enucleation of the adrenal glands was carried out in 70 adult female rats. In 30 animals of this group complete hypophysectomy was performed; in 10 additional animals the posterior lobe and half the anterior lobe of the pituitary were removed. The remaining 30 animals were not hypophysectomized. One hypophysectomized and 1 non-hypophysectomized rat were killed daily for 28 days after operation. All of the partially hypophysectomized, adrenal-enucleated animals were killed 30 days after operation. In this experiment the glands were not weighed at necropsy.

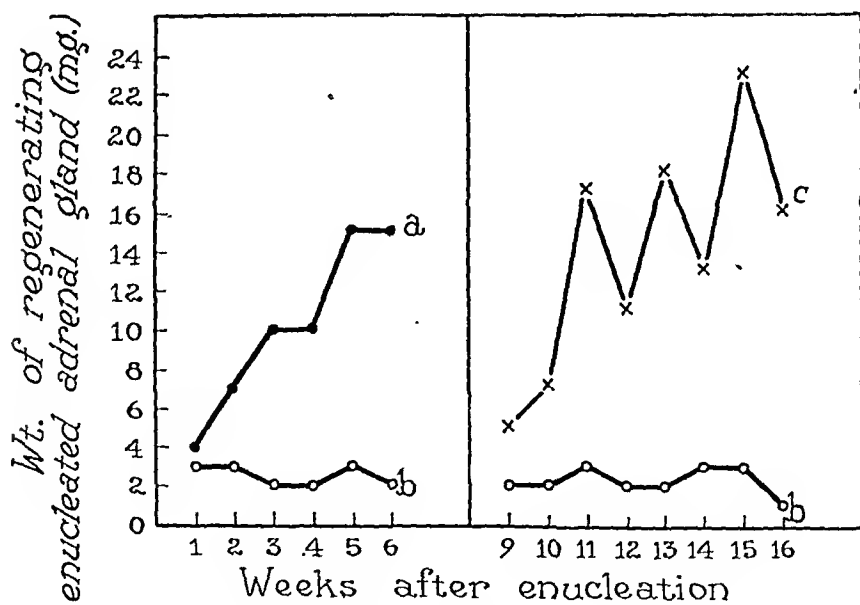
In Experiment 4, we compared the effect of the presence or absence of the right adrenal gland on the extent of regeneration in the enucleated (left) gland of 6 pairs of newborn female rats and of 8 pairs of female rats which were more than 2 years of age. In this experiment the glands were not weighed at necropsy.

Results. The results of Experiment 1 are summarized in Fig. 1 and in Table 1. When the right adrenal gland was removed regeneration proceeded rapidly from the remaining capsule of the left adrenal gland. At 5 to 6 weeks after enucleation cortical masses weighing 14 to 16 mg. had regenerated from the remnant which had remained (Figs. 1*a* and 3). When the right adrenal gland was left in place, regeneration of cortical tissue in the enucleated gland did not occur to an appreciable extent. Since approximately 3 mg. of tissue had been left at operation, and since the weights obtained (Fig. 1*b*) did not exceed that figure, it seemed clear that no significant amount of regeneration occurred during the period of 4 months. Stained sections of these adrenal capsules removed 4 months after enucleation showed some few, very small discrete masses of cortical tissue. When the right adrenal gland was left intact for a period of 2 months and was then removed from the animal, immediately the capsule which had been relatively inactive for 8 weeks was

stimulated to cortical proliferation, so that in 1 week a cortical mass weighing 5 mg. was recovered. After 7 and 8 weeks the adrenal cortical masses weighed 23 and 17 mg., respectively (Fig. 1c).

TABLE 1.—WEIGHTS (MG.) OF REGENERATED ENUCLEATED ADRENAL GLANDS AS INFLUENCED BY THE PRESENCE OR ABSENCE OF THE OPPOSITE GLAND.

Time (weeks).	Right adrenal removed at time of enucleation.	Right adrenal present.	Right adrenal removed 2 months after enucleation.
1	4	3	
2	7	3	
3	10	2	
4	10	2	
5	16	3	
6	16	2	
7			
8			
9		2	5
10		2	7
11		3	17
12		2	11
13		2	18
14		3	14
15		3	23
16		1	17



- Opposite gland removed at time of enucleation
- Opposite gland present
- × Opposite gland removed two months after enucleation

FIG. 1.—Weights of regenerated enucleated adrenal glands at various intervals following enucleation.

The results of Experiment 2 are summarized in Figure 2 and in Table 2. It was again demonstrated that the presence of one

TABLE 2.—WEIGHTS OF REGENERATED ENUCLEATED LEFT ADRENAL GLAND.

Group.	No. of animals.	Weight of gland (mg.) after 3 weeks.	Average weight.
I. Right gland removed	12	7, 8, 9, 10, 10, 11, 12, 13, 13, 13, 13, 14	11.1
II. Right gland intact	10	1, 1, 1, 1, 2, 2, 2, 2, 2, 3	1.7
III. Right gland removed*	6	3, 3, 4, 5, 5, 8	4.7
IV. Right gland removed†	10	1, 1, 1, 1, 1, 1, 1, 1, 1, 3	1.2

* 2 cc. of cortin administered subcutaneously every 8 hours.

† 5 cc. of cortin administered daily to each rat in drinking water.

intact adrenal gland will effectively inhibit regeneration of the enucleated gland, whereas regeneration occurs rapidly when the intact adrenal gland is removed. Experiment demonstrated that 5 cc. of cortin per day added directly to the drinking water was adequate

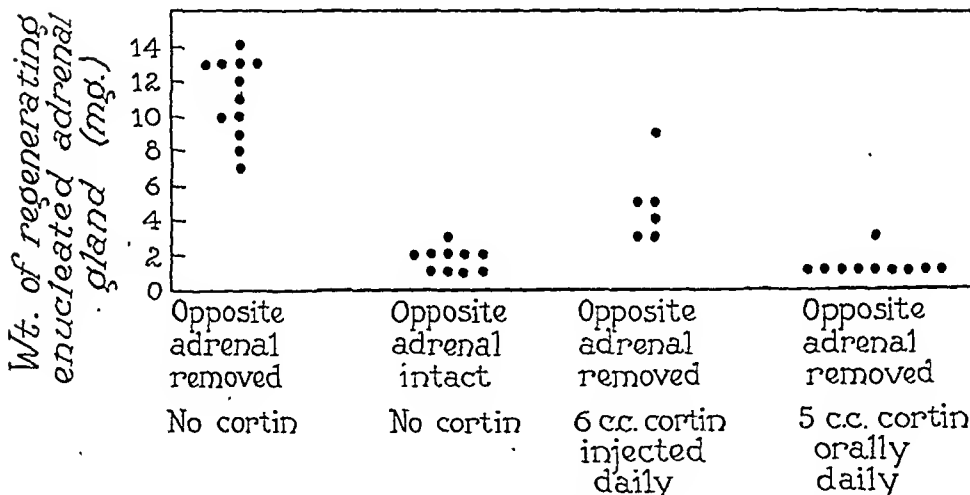


FIG. 2.—Weights of regenerated enucleated adrenal glands 3 weeks after enucleation.

to suppress completely the regeneration of the left adrenal gland even when the right adrenal gland had been removed (Fig. 4). Other data which are not reported here have shown that when smaller amounts of cortin were administered, the enucleated adrenal gland regenerated varying amounts of cortical tissue. When given by subcutaneous injection, cortin was less effective than when given by mouth. The daily administration of 6 cc. of cortin parenterally was inadequate to prevent some degree of regeneration in the enucleated gland (Fig. 2).

No quantitative data are presented for Experiment 3, since the extent of regeneration was an "all or none" response. When both adrenal glands were enucleated at the same time, regeneration of

cortical tissue followed very rapidly in the case of those animals that were not hypophysectomized. In a few weeks, masses of cortical tissue equal in size to, or larger than, the amounts of cortical tissue in the original glands had been restored. When the pituitary glands were completely removed at the same time that both adrenal glands were enucleated, regeneration of cortical tissue did not occur. Histologic comparison of the enucleated glands from the hypophysectomized animals with the enucleated glands of the non-hypophy-

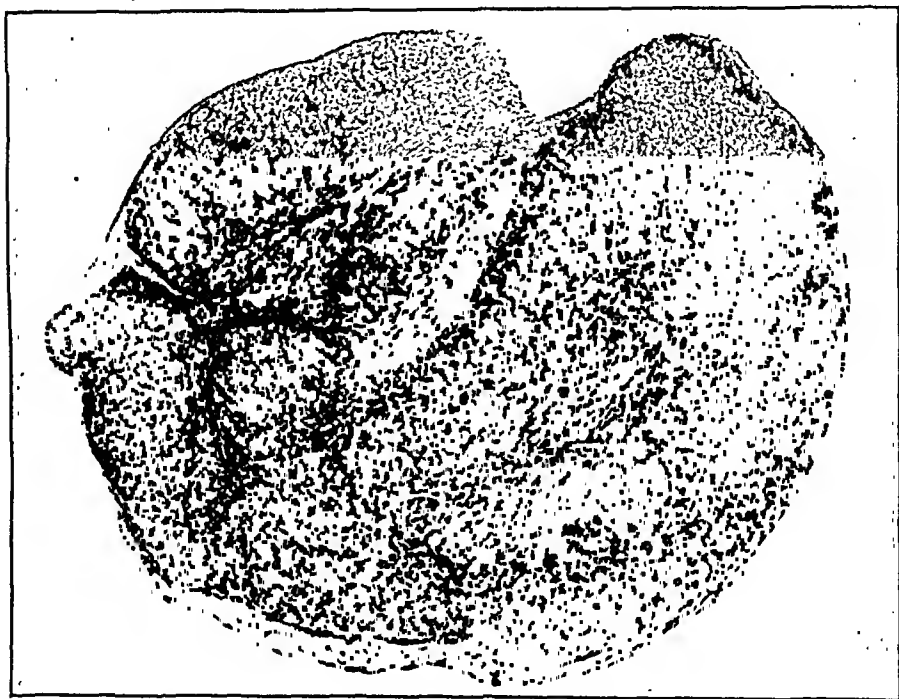


FIG. 3.—Regenerated adrenal gland 5 weeks after enucleation and removal of the opposite gland. ($\times 30$.)

sectomized animals fully confirmed this conclusion. In the hypophysectomized animals there was occasionally observed a viable capsule and small portions of cortex approximately equal in amount to that left at operation. In animals in which half of the anterior lobe remained, regeneration of the enucleated glands occurred to approximately the same extent as in the non-hypophysectomized animals.

In Experiment 4 it was clearly shown that regeneration of the enucleated adrenal gland will occur in either the young or senile animal when the intact adrenal gland is removed. Regeneration was completely suppressed by the presence of one intact gland in the cases of both young and senile animals. No quantitative data are presented since histologic examination of the tissue showed clearly that regeneration of cortical tissue in this experiment was an "all or none" response.

Comment. It seems clear from these results that the presence of one intact adrenal gland will suppress regeneration of cortical tissue in the other enucleated gland. This observation confirms the earlier observations of Wyman⁴ and of ourselves³ that an autograft of an adrenal gland will not regenerate when the other, or even a part of the other gland is left in place.

These observations further show that the daily administration of cortin was equally effective in suppressing regeneration of the enucleated gland. The cortin used in these experiments was an active, well standardized preparation which had been shown by the Ingle rat test to increase the work performance of adrenalectomized rats when administered in amounts of 0.2 cc. twice daily. It is



FIG. 4.—The enucleated gland in an animal from which the other intact gland had been removed, 3 weeks after operation; 5 cc. of cortin given daily by mouth. ($\times 30$.)

significant that large amounts of cortin were required to suppress cortical regeneration entirely. Normal amounts of cortex regenerated when minimal maintenance doses of cortin were given. Even amounts which increased work performance following total adrenalectomy failed to inhibit regeneration. Five cubic centimeters of cortin a day administered orally was required to suppress it completely.

Many investigators have been unable to restore all of the functions associated with the adrenal cortex by giving cortin. It is quite probable that insufficient amounts of cortin were given, for a wide difference exists between the minimal amounts of cortin essential for life and the amounts essential for completely normal physiologic activity. Furthermore, in the usual attempts at replacement therapy, intermittent injection is substituted for what is probably a continuous secretion of the normal gland. It is reasonable to assume that large amounts of hormone may be lost by the organism when it receives intermittent injections. In this and other unpublished data we have confirmed the observation of D'Amour and Funk¹ that cortin may be more effectively utilized when given to

the rat in its drinking water than when given parenterally. Likewise we have noted that cortin is more effectively utilized by rats when it is dissolved in oil than when it is dissolved in water.

Our observation that regeneration of the adrenal cortex does not occur in hypophysectomized rats confirms Wyman's report that transplanted adrenal glands will not become established in hypophysectomized rats. We believe that regeneration of adrenal tissue is stimulated by the adrenotropic principle elaborated by the anterior pituitary, and that regeneration will not occur when this hormone is absent. We have not, however, confirmed Wyman's deduction that the extent of regeneration of the adrenal gland is uninfluenced by the administration of cortin.

It may be important that the adrenotropic function of the anterior pituitary was still adequate when the anatomic association of the pituitary to the hypothalamus was broken by removal of the posterior lobe. Whether the anterior pituitary is self-sufficient in its regulatory functions has not been satisfactorily proved. It may be deduced from these observations that its normal anatomic relationship to the hypothalamus (involving possible nervous control) is not essential for it to secrete its adrenotropic principle.

Summary and Conclusions. A study has been made of some of the factors which regulate the regeneration of cortical tissue after the medulla and most of the cortex of the adrenal glands of white male rats had been removed. The following conclusions have been reached:

1. When one adrenal gland is enucleated and the other removed, adequate cortical regeneration proceeds within the enucleated gland.

2. When one adrenal gland is enucleated and the other left intact, there is no, or only very slight, regeneration within the enucleated gland. The presence of one functioning gland suppresses regeneration within the other enucleated gland.

3. If a normal adrenal gland is removed 8 weeks after the other gland had been enucleated, regeneration within the enucleated gland is then stimulated to occur in the normal way.

4. The oral administration of 5 cc. of cortin daily, completely suppresses regeneration within an enucleated gland, even when the other adrenal gland has been removed.

5. The subcutaneous administration of amounts of cortin comparable to those given by mouth will restrict, but not completely suppress, cortical regeneration within the enucleated gland.

6. Hypophysectomy coupled with bilateral enucleation of the adrenal glands completely suppresses regeneration of cortical tissue. In the presence of half of the anterior lobe of the pituitary there is normal regeneration in the enucleated adrenal gland.

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THE EFFECTS OF A PRESSOR SUBSTANCE OBTAINED FROM THE KIDNEYS ON THE RENAL CIRCULATION OF RATS AND DOGS.*

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IN 1898, Tigerstedt and Bergman⁸ reported that the injection of extracts of kidneys of rabbits caused a moderate and well-sustained elevation in blood pressure. Their observations have subsequently been confirmed by several groups of investigators, including Bingel and Strauss,² Bingel and Claus,¹ Hessel and Hartwich,⁵ Harrison, Blalock and Mason³ and Prinzmetal and Friedman.⁷ The initial observations by Tigerstedt and Bergman and by Bingel and Strauss indicated that the pressor principle was a large molecular substance of protein nature, being non-dialysable, insoluble in various organic solvents and precipitated by ammonium sulphate in proper concentration. More recently Hessel and Hartwich,⁵ studying renal press juice, allowed to autolyze in an incubator, found that after several days a highly active small molecular pressor substance appeared. J. R. Williams, Harrison and Mason⁹ found that a non-specific pressor agent developed when organs other than the kidney were allowed to undergo digestion. The non-specific pressor substance was found to have the chemical and pharmacologic properties of tyramine and was believed to be tyramine or some closely related substance. However, the latter authors, in agreement with previous workers, found that "renin" (the name given to the large molecular renal pressor substance by Tigerstedt and Bergman) was present in significant quantities only in the kidney. It therefore appears that under different conditions two different blood pressure raising principles may be obtained from renal tissue, one of them being of protein nature and specific for the kidney; the other probably being an aromatic amine and not specific.

At the present time information is lacking as to whether these two pressor substances are in any way concerned in the regulation of vascular tonus in health or in disease. Since the kidney seems, on the basis of the available evidence, to be the only source of one of them and to be one of the possible sources of the other, one might expect that any vascular action which these agents have would be particularly pronounced on the renal vessels. The object

* This investigation was aided by grants from the Division of Sciences of the Rockefeller Foundation, and from the Josiah Macy, Jr., Foundation.

of the experiments to be reported was to study this question. A few observations have been made concerning the action of tyramine but most of the work has been concerned with investigation of the effects of "renin" on the renal blood flow, the volume of kidney and the rate of urine formation.

Material. Fresh pig kidneys were obtained from the slaughter house and the cortex separated from the medulla, which was discarded. After the cortex had been put through a meat grinder, 20 gm. aliquots were ground with carborundum to a fine paste. Nine volumes of 95% alcohol were then added gradually, the paste being ground further during this addition. The mixture was then placed in large centrifuge tubes and allowed to stand in the ice box for 1 or more days. Shortly before the renal extract was to be injected the alcohol-kidney mixture was centrifuged, the alcohol discarded and the residue dried by spreading it out in a thin layer on a flat plate. After the kidney residue had been dried into a powdery state it was ground in a mortar with an amount of water equivalent to 2 cc. per gm. of original kidney cortex. This mixture was centrifuged and the supernatant fluid employed for injection. In order to determine whether the effects observed were specific for renal extracts injections were made of similar preparations from liver and from spleen.

Experiments on Rats. Large white rats weighing 300 gm. or more were anesthetized by the intraperitoneal injection of sodium pentobarbital—4 mg. per gm. of body weight. The abdominal aorta was then cannulated, heparin was injected and blood pressure recorded with a small-bore mercury manometer. A calibrated pipette was attached to a metal cannula inserted into the vena cava immediately below the renal veins. The vena cava was then freed just above the point of entrance of these veins so that it could be occluded at will with a bull-dog clamp. Measurements of renal blood flow were made by suddenly clamping the cava and at the same time removing the clamp between the venous cannula and the pipette. The time required for the column of blood to pass between two marks on the pipette was noted. After such a measurement the clamp on the cava was removed allowing the blood in the pipette to return to the circulation and the renal venous return to proceed along the normal channels. Following several measurements renal extract was injected through a side connection of the aortic cannula and its effect on the blood pressure and the blood flow through the kidney noted. The volume of renal extract injected was 0.5 to 1 cc. For purposes of control similar volumes of 0.9% sodium chloride solution were administered alternately with the injections of the renal extract.

Results With Rats. Satisfactory preparations were obtained with 3 rats, 7 injections of "renin" and of saline, respectively, being made. Significant rise—i. e., of more than 10 mm. of mercury—in blood pressure occurred twice following the injection of salt solution, the increase being evanescent. Significant increase in blood pressure occurred 5 times following injection of "renin," the rise being well sustained in each instance. The initial administration of "renin" was followed in each rat by a well-marked and sustained increase in blood pressure, subsequent injections producing less effect. In each instance the increase in blood pressure produced by renal extract was preceded by a marked but transient decline lasting only a few seconds. (The substance or substances respon-

sible for this initial decline in blood pressure is not "renin" for this depressor effect occurs following the administration of similarly prepared extracts of organs other than kidney. Since the method of preparation makes the presence of histamine and other small molecular pressor substances unlikely, it seems probable that the initial depressor effect is due to peptones, but of this point we are not certain.)

The administration of salt solution caused in each of 7 instances a slight increase in the renal blood flow. The injection of "renin" was, on the other hand, followed in each of the 7 observations by a pronounced and sustained diminution in the renal blood flow. This diminution was maximal at a time when the blood pressure was above the level before the injection. It persisted after the

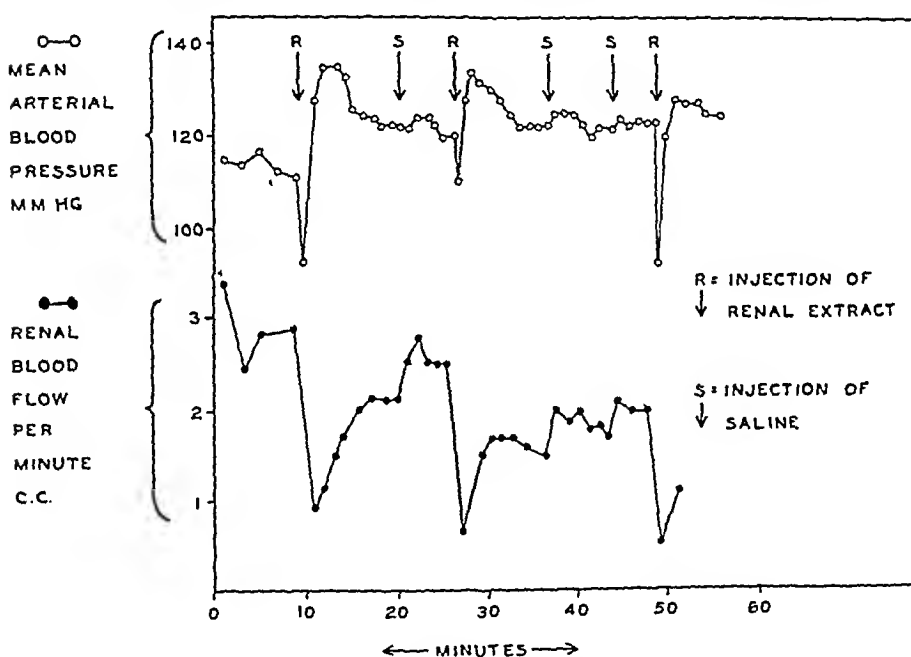


FIG. 1.—The administration of renal extract ("renin") to rats caused rise in blood pressure and decline in renal blood flow, the latter effect being more prolonged. (The initial decline in blood pressure was apparently due to impurities as it occurred when extracts of other organs were injected.)

blood pressure had returned to the previous level, and occurred even when the pressor response to renal extract was minimal. The changes in blood pressure and in the renal blood flow are illustrated in Fig. 1.

These experiments suggest that the large molecular pressor substance (Tigerstedt's "renin") has a pronounced action on the blood-vessels in the kidney. In order to localize more definitely its site of action, attempts were made to measure the urine flow

and the kidney volume of rats. Such attempts were not successful and accordingly further experiments were undertaken on larger animals.

Experiments on Anesthetized Dogs. Dogs weighing 12 to 16 kg. were anesthetized by the intravenous injection of sodium pentobarbital, 30 mg. per kg. of body weight. The renal blood flow was measured by passing a specially constructed cannula into the inferior vena cava through the external jugular vein, according to the technique devised for the coronary blood flow by Harrison *et al.*⁴ and modified for measurement of the blood flow through the kidneys by Mason *et al.*⁶ Heparin was used as an anti-coagulant. The blood pressure in the femoral artery was recorded with a mercury manometer. In some of the experiments a plethysmograph was inserted on one of the kidneys through a flank incision, and in a few instances urine was collected from a catheter in the bladder. After several preliminary measurements of the blood flow through the kidneys renal extract was injected and its effect on the several functions noted. The amount of the extract injected varied in these experiments from 10 to 40 cc., corresponding respectively to from 5 to 20 gm. of renal cortex. In order to determine the effects of the injection of equivalent volumes of fluid and to learn whether the effects observed were dependent on substances present only in the kidney, 3 experiments were done in which extracts of liver tissue prepared in a similar way to the kidney extracts were administered. A number of observations were also made concerning the action of tyramine monohydrochloride (Pfansthiel), which was administered in doses of 0.5 to 1 mg. per kg. of body weight.

Results With Dogs. (See Table 1 and Fig. 2.) Except for an evanescent decline in blood pressure consistent effects were not observed from the administration of the extract of liver. Kidney extract, on the other hand, usually caused increase in blood pressure, diminution in renal blood flow, some swelling of the kidney, and an

TABLE 1.—THE EFFECTS OF RENAL EXTRACT ("RENIN"), OF LIVER EXTRACT AND OF TYRAMINE ON THE RENAL CIRCULATION OF DOGS ANESTHETIZED WITH SODIUM PENTABARBITAL.

Function studied.	Source of extract.	Number of observations.	Increase.	Decrease.	No change.*
Mean arterial blood pressure	Kidney . . .	13	9	2	2
	Liver . . .	3	0	2	1
	Tyramine . .	13	13	0	0
Renal blood flow	Kidney . . .	11	1	9	1
	Liver . . .	3	0	1	2
	Tyramine . .	13	0	11	2
Volume of kidney	Kidney . . .	9	7	1	1
	Liver . . .	3	0	1	2
	Tyramine . .	10	1	8	1
Rate of urine secretion	Kidney . . .	3	3	0	0
	Liver . . .	3	1	1	1
	Tyramine . .	2	0	1	1

* Changes of less than 10% in the rate of blood flow and of urine formation and of less than 10 mm. of mercury in arterial blood pressure were not considered significant. In compiling the table, evanescent diminution in blood pressure occurring immediately after the injection of tissue extracts and disappearing in 1 or 2 minutes have been neglected.

increase in the amount of urine formed. These changes were not encountered in every experiment, which is not surprising in view of the impure character of the extracts. Tyramine caused well-marked elevation of blood pressure, diminution in the renal blood flow, and shrinkage of the kidney.

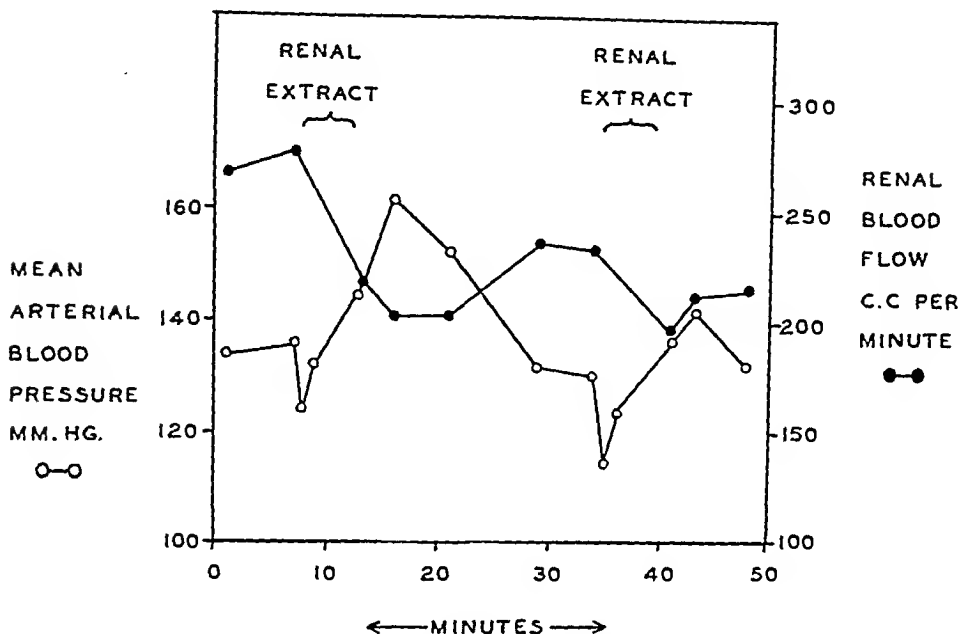


FIG. 2.—The administration of renal extract ("renin") to dogs caused rise in blood pressure and decline in renal blood flow the latter effect being more prolonged (The initial decline in blood pressure was apparently due to impurities as it occurred when extracts of other organs were injected.)

Observations on the Rate of Urine Formation in Unanesthetized Dogs. It was not possible to measure renal volume and renal blood flow in unanesthetized animals, but it was thought that some indication could be obtained of the functional changes in the kidney of normal animals by measurements of the amount of urine formed after the administration of renal extract or of tyramine. Accordingly a series of such experiments were undertaken, urine being collected by a catheter in the bladder, and the volume excreted during each 5-minute period noted. In some of the experiments, 400 cc. of water were given the animals by stomach tube at the start of the experiment, while in other instances no fluid was given. After the urine volume had been relatively constant during several successive 5-minute periods, intravenous injections of renal extract, liver extract, splenic extract or of tyramine were made. Only 1 injection was made into a given dog on the same date but the same group of animals was used throughout the study. The results of

these observations are summarized in Table 2. Constant effects were not obtained from the extracts prepared from the liver or spleen. On the other hand, in most of the experiments the kidney extracts resulted in a slight to well-marked diuresis, while tyramine caused diminution or no change in the amount of urine secreted.

TABLE 2.—THE EFFECTS OF RENAL EXTRACT ("RENIN") AND OF TYRAMINE ON THE RATE OF URINE FORMATION OF UNANESTHETIZED DOGS.

Source of material injected.	Number of experiments.	Effect on urine flow.			Remarks
		Increase.	Decrease.	No change.	
Kidney	8	6	1	1	No additional fluid given.
Kidney	8	6	1	1	400 cc. of water given by stomach tube before experiment.
Spleen	7	2	2	3	
Tyramine	5	0	3	2	

Comment. Since tyramine caused diminution in renal blood flow and shrinkage of the kidney in spite of a well-marked increase in the blood pressure, it seems likely that this substance causes contraction of the afferent glomerular arterioles or possibly of the small arteries in the kidney.

The interpretation of the results observed after the injection of "renin" is less certain. It seems clear that the renal extract had effects which were different from those of the similarly prepared extracts of liver and spleen. However, one cannot be sure that the alterations in the different functions studied were all due to the substance which caused elevation of blood pressure, because the extracts were not sufficiently purified. With this limitation in mind the findings are interpreted as indicating that since the renal extract produced swelling of the kidney, diuresis, and diminution in renal blood flow in spite of elevated blood pressure, it probably caused contraction either of the efferent glomerular vessels or of the smaller renal veins. Whether the diuresis observed is to be accounted for as the result of an increase in glomerular filtration because of elevated intracapillary pressure, or should be ascribed to diminished reabsorption of fluid by the tubules is not clear from the experiments. In any case, the experiments on dogs as well as those on rats suggest that renal extract has an especially pronounced and prolonged effect on the blood-vessels of the kidney, because the diminution in renal flow persisted for some time after the blood pressure had returned to normal (Figs. 1 and 2).

The results reported are confirmatory of the findings published by Bingel and Claus in 1910.¹ These authors, working with material obtained by the addition of ammonium sulphate to renal press juice, observed increase in blood pressure, swelling of the kidney, shrinkage of the leg and diuresis in rabbits.

Summary. Tyramine caused increase in blood pressure, diminution in renal blood flow, shrinking of the kidney and either no change

or a diminution in urine volume. This substance is believed to cause contraction of the afferent glomerular vessels.

Renal extract (Tigerstedt's "renin") caused increase in blood pressure, diminution in renal blood flow, swelling of the kidney and increase in the excretion of urine. Granting the possibility that some of these alterations are due to impurities rather than to the action of the pressor principle, the experiments suggest that the latter substance produces contraction of the efferent glomerular vessels. Constant changes in the several functions studied were not encountered following the administration of similarly prepared extracts of the liver and of the spleen.

The vessels of the kidney appear to be particularly susceptible to the action of renal extract, for the diminution in renal blood flow which followed the administration of this extract was usually more pronounced and of greater duration than was the elevation of blood pressure.

The experiments throw no light on the question as to whether the renal pressor substance is of any significance in health or in disease.

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TYPHUS FEVER IN PENNSYLVANIA.

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TYPHUS fever was first clearly recognized and differentiated from typhoid fever by Gerhard,⁷ of Philadelphia, in 1836. Some of the great epidemics of Europe, recurring since the 16th century, have been due to it. The disease in epidemic form has never been common in Pennsylvania, although occasional outbreaks in Philadelphia have occurred in connection with the arrival of immigrants from Europe. The last outbreak recorded in Philadelphia was in 1883¹⁶ since when no further mention is made of epidemic typhus in this state. Despite the absence of epidemic typhus in Pennsylvania and other sections of this country in the present century, students of the disease^{1,4,8,12} in America have found that it occurs endemically in

certain localities under circumstances which would seem to exclude the likelihood of recent importation of the virus from abroad. Since 1910,¹ the term Brill's disease, has been used to designate the type of typhus which is endemic in this country, although the name is gradually being replaced by that of endemic typhus. The disease is now readily differentiated from typhoid fever, but in Pennsylvania⁶ during the past few years another typhus-like disorder, Rocky Mountain spotted fever, has been confused with it. The purpose of this paper is to present the incidence of endemic typhus in Pennsylvania, and to report 3 cases recently studied at this hospital, in order to emphasize the salient features of the disease. Although these cases appear in the archives of this hospital as being endemic typhus, it will be seen from the following, that the first and possibly the second case are more probably instances of Rocky Mountain spotted fever.

The first report of endemic typhus in Pennsylvania was by Lewis¹⁰ in 1911, at which time he presented 13 cases of so-called Brill's disease treated at the Pennsylvania Hospital. Six of these cases occurred in 1907, although they were not recognized as such until Brill's report in 1910. Three years later Roussel¹⁶ (1914) published 4 additional cases and in 1931 he⁵ mentions 10 more cases from Philadelphia. The above 27 cases, all from this city, constitute the incidence of endemic typhus in Pennsylvania as recorded in the literature. According to recent statistics of the Pennsylvania Department of Health² only 2 cases of the disease have been reported in this state since 1906, but unfortunately no data are available concerning these, except that the cases occurred in 1913 and 1914 respectively. We have presented (Fig. 1) the incidence of the disease, as recorded by the health departments^{2,9,11,14,15,17,18} in Pennsylvania and the states which bound it, during the past 5 years. We believe that the incidence of the disease is greater in this state than the above data indicate, due possibly to faulty diagnosis or to failure to report the disease.

How long endemic typhus has existed in this state, and how extensive has been its spread elsewhere, is uncertain. It is known, however, that the disease is widespread among rats and is transmitted to man by the bite of infected fleas. The *Xenopsylla Cheopis* (rat flea³) is considered the principal vector of the disease from rat to man and has been shown to be most prevalent during the fall season when the incidence of typhus is greatest. During a recent survey¹⁹ of the port of Philadelphia, it was found that 60% of all fleas captured over 19 consecutive months belonged to this species with their highest incidence during the fall months. The Norway rat, regarded as the chief reservoir of the disease in this country, was the only species represented among 2765 rats captured at that time. Since these infected vectors usually remain undetected until man contracts the disease, the epidemiologic character

and the geographic distribution of the disease is based primarily on human case reports.

Endemic typhus may be briefly defined as an acute, infectious, but non-contagious disease, usually seen in late summer and fall, showing no predilection for the lower strata of society, and is widespread among rats being transmitted to man by infected fleas. Clinically it is characterized by sudden onset with chills, a continued fever terminating usually by rapid lysis about the fifteenth day; headache, weakness, a macular eruption which appears about the fifth day on the chest and abdomen, then spreading over the upper arms and thighs, but rarely involving the palms and soles and almost never the neck and face. Convalescence as a rule is

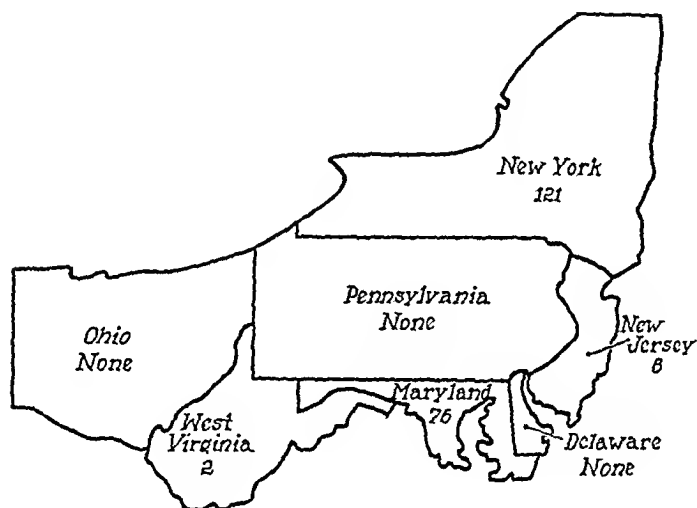


FIG. 1.—The incidence of typhus fever, as recorded by the Health Departments in Pennsylvania and the states which bound it, during the past five years.

rapid and complications seldom occur. The mortality of the disease is about 3% with an atypical pneumonia the chief cause of death. The pathologic findings¹³ are referable to the vascular system, where endothelial proliferation is followed by thrombosis and a perivascular accumulation of macrophages and lymphocytes, particularly in the skin, brain, heart, spleen, and lymph nodes.

Although the clinical course and the character of the exanthem leads one to suspect the disease, the diagnosis must be confirmed by laboratory studies. The total white count usually falls within normal limits, although a leukopenia is often seen and occasionally a slight leukocytosis in uncomplicated cases will occur. The hemoglobin and red cells do not show much variation. The urine shows changes common to other fevers. At some stage of the disease, usually by the end of the second week, the blood contains sufficient

specific agglutinins for proteus X-19, as demonstrated by the Weil-Felix reaction.

The Weil-Felix reaction is also positive in Rocky Mountain spotted fever. Typhus fever, a flea-borne infection, occurs usually in late summer and fall in urban districts. The rash is first noted on the chest and abdomen, and although it frequently spreads to the upper arms and thighs, it seldom involves the palms and soles and almost never the neck and face. Rocky Mountain spotted fever, a tic-borne infection, is most commonly seen in the late spring and summer months in rural communities. The rash makes its first appearance on the wrists and ankles, with rapid extension over the entire body including the palms, soles, neck and face. If necessary, guinea-pig inoculation and cross agglutination tests are available through the Public Health service.

Since typhus fever is self-limited, and specific therapy unknown, symptomatic treatment and supportive measures must be relied upon. Various attempts at prophylactic vaccination have been made, but the use of a living virus as a vaccine has been proven dangerous. The obvious prevention for the disease, since it is carried by rats and transmitted by rat fleas, is the destruction of rats and rat harbors.

We have included in the following case reports the pertinent features of the histories and the positive physical and laboratory findings. Blood and urine cultures as well as repeated Widal agglutinations were negative in each instance (Fig. 2).

Case Abstracts. CASE 1.—J. M. (34-17543), a 19-year-old white male, was admitted to this hospital on June 18, 1934. On the day before admission he complained of a severe headache, generalized body pains and soreness of the eyes; followed on the next day by sore throat, fever, diplopia, tinnitus, stiffness of the neck and a definite convulsion. The patient admitted having been bitten by tics about 2 weeks prior to his illness while working in the immediate vicinity of his home, which was approximately 35 miles from Philadelphia.

Physical examination revealed an acutely ill boy with a profuse pink maculopapular rash over the entire chest, abdomen and extremities but not involving the soles, palms, neck and face. There was moderate redness of the throat and some neck rigidity. After admission, the pyrexia, rash, and neurologic symptoms persisted until about the fifteenth day of the illness, at which time the rash had completely disappeared and the elevation in temperature subsided almost by crisis. The patient made an uneventful recovery being discharged on July 15, 1934.

CASE 2.—W. L. (35-19833), a white male, aged 53, was admitted on May 12, 1935. The present illness began 6 days before admission, with pain in the left shoulder, followed in 2 days by general malaise, fever (102°), severe headache and backache. On the fourth day of illness there appeared a rose-colored rash involving the chest and abdomen. The pyrexia (102-104), headache and rash persisted until admission on the sixth day of the disease. He had not been out of Philadelphia for several months prior to his illness and denied any knowledge of contact with tics or any rat infestation in his home or at his place of business.

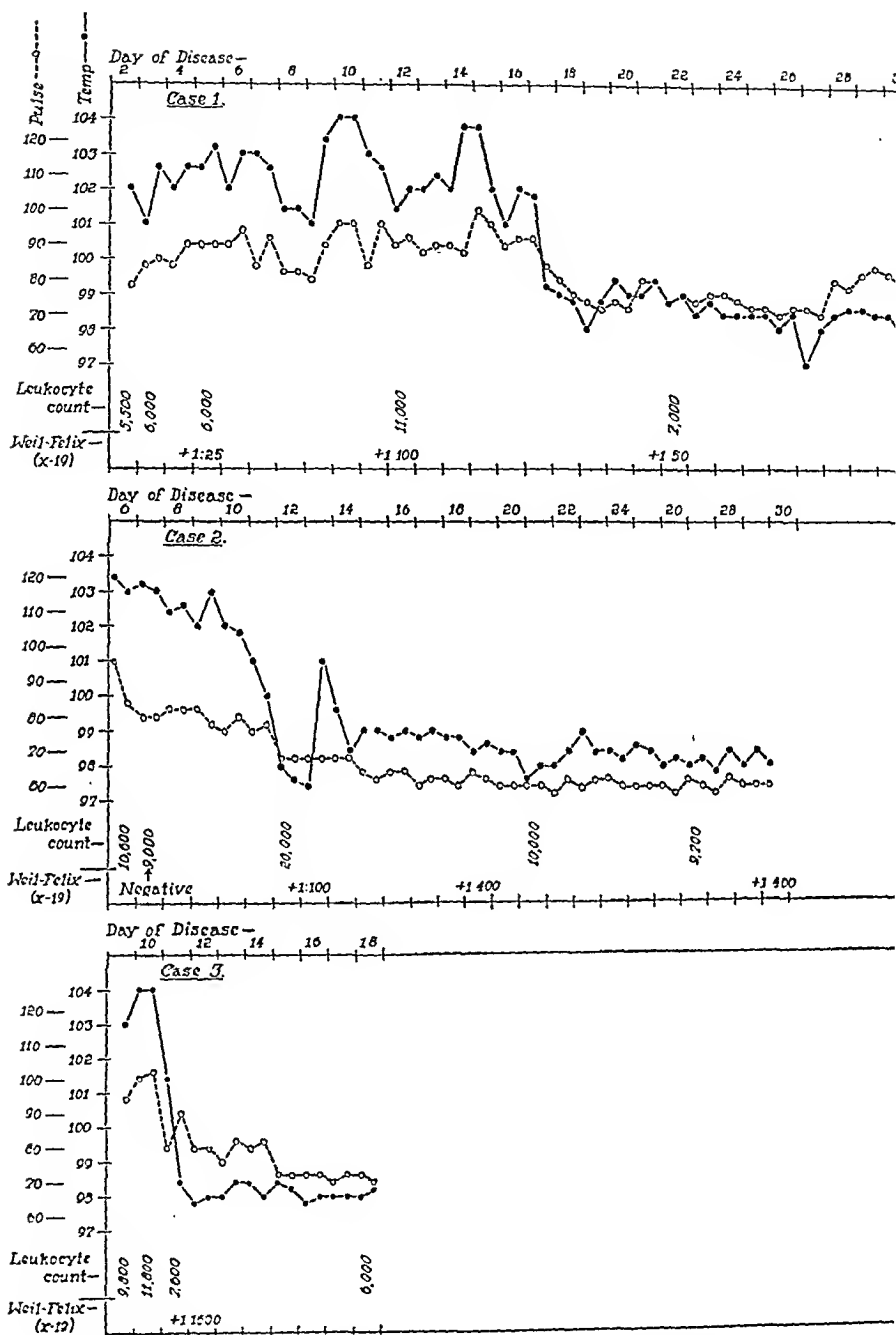


FIG. 2.—Showing days of disease, temperature ranges, pulse rates, leukocyte count and Weil-Felix agglutination reactions during hospitalization.

On physical examination the patient did not appear acutely ill. Over the abdomen, trunk, chest, and shoulders was a diffuse, pink, macular eruption which faded on pressure. The throat was markedly injected and the liver slightly enlarged. Following admission the symptoms continued and on the twelfth day of the disease, the patient experienced generalized abdominal pain accompanied by a sudden fall in temperature with an elevation of leukocytes and rigidity in the right abdomen. This initial drop in temperature was followed the next day by an elevation reaching 101° with physical signs of fluid in the left chest; a finding which was confirmed by Roentgen ray examination. This upset was attributed to a pulmonary embolus from a small mesenteric thrombosis. The rash had completely disappeared by the fourteenth day of the illness. Following the above complication, the patient improved gradually and at the time of his discharge, June 5, 1935, both lung fields were clear and his usual state of health resumed.

CASE 3.—G. S. (33,13215), a white woman, aged 48, was well until February 15, 1936, 9 days before admission, at which time she complained of weakness, generalized body pains, severe headache, profuse sweating, chills and fever. Five days later these symptoms were followed by a rose-colored rash involving the abdomen, chest and upper arms. The patient had remained in Philadelphia for over a year preceding her illness and although she denied rodent infestation of her home, subsequent investigations proved otherwise. We were unable to capture any of the rats on the premises, but the patient's family admitted having seen rather large rats in the basement of their home.

Physical examination revealed no evidence of acute distress. The throat was slightly injected and the abdomen and chest were covered with small pink macular lesions. After admission the patient continued to have an elevation in temperature, sweats, and severe headache. The rash had completely disappeared by the eleventh day, at which time the pyrexia subsided almost by crisis. The patient was discharged on March 3, 1936, after an uneventful complete recovery.

As stated above, the first and possibly the second case represent instances of Rocky Mountain spotted fever rather than endemic typhus. In the first case, the illness occurred during June in a rural community with a history of tic bites followed by rather severe cerebral manifestations. The illness in the second was during the spring although the patient lived in an urban district and denied any history of contacts with tics. Both cases, however, lacked the typical distribution of the rash as well as the necessary laboratory studies to differentiate between endemic typhus and Rocky Mountain spotted fever. It is probably that certain cases reported in the past as Brill's disease or endemic typhus would now be considered as Rocky Mountain spotted fever. Since we lack the necessary laboratory data for an accurate differentiation of these typhus-like infections, we are including all cases in this report with the diagnosis of endemic typhus both from the literature and the records of this hospital. Of the 30 cases with this diagnosis, 29 occurred in Philadelphia. The data at hand indicate a focal distribution in Philadelphia, but sufficient information is not yet available for an accurate delineation of infected localities within Pennsylvania.

Summary. 1. The incidence of endemic typhus in Pennsylvania as recorded in the literature is presented.

2. A comparison is made of the number of cases reported to the health department in this and surrounding states during the past 5 years.

3. Three cases studied at this hospital and diagnosed as endemic typhus are reported.

4. The differential diagnosis between the typhus-like diseases in this state is discussed.

5. Physicians should be aware of the presence of this disease in Pennsylvania, especially in Philadelphia, during the late summer and fall months.

6. The importance of reporting all cases as an aid in the epidemiologic study of the disease is stressed.

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DISEASE AND THE NEGRO.*

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OBSERVATION of the negro's body brings to our attention many points wherein he differs from the white man. The colored skin, the tightly curled hair, the protruding eyeballs, suggestive of hyperthyroidism, are some of these points. The silhouette of the negro's head with the slanting forehead, tendency to enlarged frontal sinuses

* This contribution is the foreword of a book of the same title upon which the authors are at present engaged.

and heavy protruding mandible brings out other well-known characteristics. Pictured by the Roentgen ray, the bones of the negro can commonly be recognized as such by the thickened walls of the calvarium, the narrow pelvic outlet in the male, and the bony protuberances on the humeri and pubic arches which serve as points for muscle attachments.

Contrary to the general belief, the hands of the negro are frequently smaller than would be expected when we consider the size and strength of his body. Full-grown men of this race of unusual power and muscular development are seen presenting the hands of a 16-year-old boy. It has been an observation in the Employees Hospital for years that the so-called artistic hand with its slender tapering fingers is a common possession of negro women. These variations in form are all structural differences guided no doubt by complex glandular activities to which at the present time we have no key.

When we consider the two races in motion, we find more important differences. The negro is more lethargic in his movements. His gait inclines toward a shuffle. There is a slackening of the knee-joints suggestive of a man walking with skis. The force of gravity seems to act with greater power upon the negro than it does upon the white. He rarely rises upon his toes. His activities in the prize ring past and present bring out this point in a striking way. In the parlance of pugilism all great negro fighters have been "flat-footed fighters." They have produced results by shuffling in toward their opponents bearing their whole weight upon the flattened foot.

We have never been able to believe that the diseases of the two races as such, differed in any essential detail. Many thousands of laboratory tests performed here during the past 18 years have produced similar results in the 2 races. Throughout the whole gamut of diagnostic research as represented by basal metabolic estimations, blood chemistry determinations, and the other various techniques which are commonly employed, the normal findings have been identical. Differences found in the negro as in the white have been differences due to his age, sex, economic condition and other factors. We have never been able to find any true racial differences. Nor have we been able to find in the work of others similarly engaged, proof of any such differences.

Nevertheless, it has been the observation of those who have directed their attention toward this problem, that the disease patterns of the two races differ in many respects. Indeed, if our perceptions had not been lulled by a constant repetition, the differences in both morbidity and mortality rates relating to sickness as it occurs in the two races would be regarded as startling. This has been common knowledge for some time. So far as we know, no explanation has ever been presented which suggested the existence of a common denominator. It is true that obvious conclusions

have been drawn from separate instances. The sexual promiscuity of the negro has led to his syphilization. The sparsity of his diet has led to outbreaks of pellagra. These are merely explanations of episodes. They cannot solve to anyone's satisfaction the broad problem. Such relations deal only with separate entities and it will be noted with positive factors only. At best, they are connected with the increased occurrence of disease which, as we shall see, portrays only a part of the picture. The problem under discussion is more intricate than that.

We have felt that there was some common cause which operated both toward the increased frequency of some diseases, and the diminished frequency of other diseases among our colored patients. Early in our search we became aware that consideration of disease in the negro entails an oblique consideration of disease in the white man. We have felt that through this obliquity of approach, profitable implications might be unearthed regarding the latter's problem also. Not that we need any such goad. The search, if confined to the negro alone, would require more intelligence than any one set of observers could possess.

Since a search of all clinical and laboratory records proved barren of results in producing evidences of true racial differences in regard to disease, we turned to other sources for enlightenment. To guide us in this quest has been the impression, a persistent one, that the search has been founded upon too narrow a base. The mental side of the picture has not received the attention it deserved. The attitude of the colored patient toward his disease, whatsoever it may have been, has not been elucidated. A circumstance of common occurrence, encountered in our daily routine, has kept recurring to our minds. Whenever we engaged in conversation with the type of negro we see in our wards, we became aware that great as were the physical differences between us they were no greater than the mental differences brought out by this simple form of human contact. This constant experience with the sick negro has convinced us that nowhere in the comparison of the psyche of the two races are there more important or momentous differences than in the ideology which each possesses regarding disease.

If we are presented with the opportunity of comparing sick white people and sick colored people, we are struck with the fact that there are widely different patterns of disease in the two races. These patterns differ not only in the circumstance that each race has its own set of diseases common to it, but also the degree of disability created by any specific type of disorder shows a variance in the two races. When we compare the cultural levels of the two groups, this is not at all surprising. The white people reflect an attitude conditioned by a greater knowledge of the subject of human sickness, incomplete though it may be.

Through their experiences in childhood, by word-of-mouth tradi-

tion which they have absorbed from their parents and older associates during their adolescence, they have at least a working knowledge of what it is all about. They have heard all the common forms of sickness described and defined. Since this subject is so often a matter of family discussion, their information from this source alone is considerable. Most of us can look back into our childhood and recall that our ideas of disease received their first definitions at that time. These definitions have persisted in the minds of many to color that side of their mentality in later life. To some the recollection of a member of his family suffering from the tortures of an acute appendix with the resulting spectacular surgical relief, remains as one of the vivid memories of their childhood.

Later as the medical profession extended its vocabulary, and its knowledge became more and more public property, ulcers of the stomach and duodenum, with their possible complications, goiter, diabetes and other sinister names took their place in the public consciousness. Ideas upon these and similar emergencies became a part of the white person's thinking life with the certainty that each one might apply such possibilities to his own instance when the occasions arose. We may take it for granted that no human being who had heard of such horrors could become aware of their proximity in the person of someone near and dear to him without the possibility of his own vulnerability becoming apparent to him. This type of knowledge, often highly inaccurate in character, became a part of the folklore of white people with any pretensions to education. Indeed it became a part of everyday education well nigh as important as the ability to read and write; for without it one was left out of the circle when discussions arose on a subject of such universal interest.

When an attack of sickness came to any white person, the very human question arose in his mind as to the identity of his complaint. As time went on and his opportunities for education along this line presented themselves, his view of the disease problem was constantly being widened, new disease names were added to his list. As the discussion of diseases progressed in the public mind through newspaper articles, advertisements, and of late through the radio, the minds of white people as a group achieved a broad scope in the consideration of the all-important matter as to what it was that was making them sick. This educational process has its good and its evil points.

Through the vigilance which it has created, many hasten to the doctor early in the course of their malady and are thus saved the dangers of delay. In a word, white people of any reasonable degree of intelligence pay at least as much attention to the state of their health as the subject merits. This is a valuable contribution to the life prolonging scheme of their lives. It is viewed as laudable and praiseworthy whenever the patient is found to be suffering from

what is known to the medical profession as an "organic disease." Such disasters it is common knowledge are amenable to cure just insofar as they are permitted an early recognition. Malignant growths, pulmonary tuberculosis, and many other thorns in the side of humanity fall into this category. If we see them early we feel that we can do them the maximum of good.

It is a fact well known to the profession, however, that all this educational campaign by which the laity have been acquainted with the ills of the flesh has been by no means an unmixed blessing. With increasing frequency we believe as time has gone on many unfortunates have been brought to such a state of vigilance in regard to the state of their health, that they are constantly on the *qui vive* toward those signs and portents which accompany the life processes of every human body. These men and women note with apprehension every variation in the rate of their heart beat. They watch with dread the changing pressures in their hollow viscera. They magnify all the physical and physiologic changes which mark the human body striving to maintain its equilibrium. According to the degree of education which they have obtained in a haphazard way they attempt to identify these trivial things as diseases. This one has a gastric ulcer, this one a goiter; in their minds at least.

This is the type of patient who outnumbers many times over the patients who seek medical advice suffering from some organic disease. To them, certainly, the vigilance in regard to their well-being created by a generation of education along medical lines has not been a boon. When we meet these people, we are immediately aware that they all have an explanation for their sickness. They have a name for their disease. More often than not, this name bears little if any relation to the truth of the matter, but they have given it a name nevertheless. Fifty years ago the nomenclature of disease was much simpler. The minds of the laity were satisfied with clichés which would never pass muster today. People in that time had "heart trouble" or "kidney trouble" or "Bright's disease" and the dreaded "dropsy." With these simple trade-names they must have been able to satisfy their minds. The physicians of the day had little more to tell them; indeed if they were honest men they must have questioned the truth of even these bare disclosures.

Today our white patients demand more from us than the simple statement of a condition. They demand proof: Roentgen ray diagnosis, chemical tests, blood examinations and what-not. They must have faith in these procedures as they are always willing to pay for them. It is this same attitude of eternal vigilance regarding their health that makes white people skeptical when all too often the examination performed with its expensive ritual, confounds the ideas which they have formed as to what ails them. If it is not a cancer that they have, then what is it? The symptoms from which they suffered, and all that they had read upon the subject and all

that they had heard, had led them to the conclusion that a cancer was what they had. It may be that they have learned too much about the problem of disease, or that the manner in which they have learned has brought them only misfortune.

When we cross the hall into a ward of sick negroes, we find that we are entering another world. Whatever may have been the early education of the negro in the definition of disease, it has left few marks behind it. If they are aware of the ills to which the flesh is heir they never mention the subject. Though we have seen thousands of negro patients in the past 15 years, we have yet to see the first one to suggest that he or she may be suffering from that bane of the white folks, an "ulcerated stomach." If they have heard the words they have long since forgotten them. Their attitude toward the organs of the body is an attitude that is free from strain and antagonism. Their attitude toward their own physiologic processes is marked by a simplicity and common sense that is far above that of the Caucasian. In the natural course of events they must have read some of the modern advertising on how to maintain their health at a proper level.

Radio commentators must rarely have consumed some of their time addressing them on the subject of vitamins and the ills which were bound to follow if their advice were not taken. The seed so far as we have been able to observe has fallen on barren soil. As a group they have refused to become concerned about the varying activities of their digestive organs, matters which are of the deepest interest to their white contemporaries. The negro takes such things as a matter of course. He lives at peace with the various parts of his body, to an extent that is only approached in the best balanced of the whites. His stomach is his friend, his intestines are organs to be left alone and not tampered with by all sorts of maneuvers. Leave such things alone, is the negro's point of view. The attitude of the negro toward all forms of sickness is one of disregard. He pays them no attention, and thus manifests his belief that in the end all such troubles will disappear.

It is this conviction on the part of the negro which is the determining factor in conditioning disease patterns as we see them affecting the two races. The great mass of symptoms without any underlying discoverable lesions which brings thousands of patients to the physician suffering from what we call "functional disorders," serve no such end in the negro's instance. He takes no such interest in the physiologic minutiae of his life as does the white. A pain in his stomach is just that; his mind is free from the multiplicity of horrors which creep unasked into the white brain whenever such a minor event threatens a white body. He can hardly consider himself as developing the deadly pains of appendicitis when he has never heard the expression or has forgotten it long since if he ever did hear it. He is spared the fear of many diseases because they have

never taken definition in his mind. Since his brain holds no image of them he cannot suffer from them.

When we look into the matter we shall find that the occurrence of what the profession calls "organic disease" is much higher in the negro than it is in the white. Not only are such misfortunes more common, but they are met in a more advanced stage. When we encounter such diseases as pulmonary tuberculosis, carcinoma, exophthalmic goiter, we find that they are disclosed as a rule only after long periods of progress. Here the disregard which the negro pays toward all forms of disease has acted to his detriment. Had he a tithe of the vigilance which the white man displays in such matters it would be greatly to his advantage.

The strength of his position is best shown when we step into that vast field of vague and indefinite symptoms personified by the type to which has been given the name of "neuro." From the terrors of this man's days with his vertigo, headache, constipation, flatulence, air-filled stomach and intestine, and anal pruritus (to name only a few of the more common symptoms) the negro is free. He is rarely found in that vast army which pauses momentarily in the physician's waiting-rooms, on their way to be cured by the quacks. All of our previous experiences lead us to the belief that from this collection of human misery, the negro has been shut off by the state of his mind. Not that he does not suffer from subjective symptoms, the same in fact which make the white man miserable, but that he pays them no attention. He has no dreaded names to give them. He has no store of ideology which provides some horror to identify with some mild abdominal complaint. We might call such a state of mind only a proof of the valor of ignorance, but to many sufferers in white skins it would be a blessed ignorance indeed.

We have always tried to bear in mind that the problem of the negro in sickness represents merely a part of the problem of his life as a whole, differing from the main pattern merely in detail. We believe, however, from what we have seen that the negro entertains a true disregard for disease patterns for reasons which we have endeavored to make clear. This disregard is not identical with his racial reticence, which conditions every relation which he has with the whites. This reticence colors his thoughts and restrains his conversation frequently to monosyllabic replies when conversing with the other race. When dealing with the white man the negro is on the defensive, and well he may be. He seems to be under the impression, which is well-founded in truth, that many white men would not engage him in conversation, or indeed pay him any attention at all, if they did not have some ulterior motive to serve.

Years of unfortunate contacts have led the negro to be on his guard with many Caucasians—not only to be on his guard, but to make a persistent study of the personalities of such members of the dominant race as his daily routine touches. In a way, the negro has

all the advantage when such contact takes place. He knows all about the white man: his habits, tastes, virtues and vices, and he has formed a shrewd estimate of his personality. This knowledge, however, he only dares to use in a negative way. He knows that not always is there an equality of footing, and all that he has become aware of in regard to the white man he will be able to employ chiefly to guide him in the protection of his own interests.

White people who have the name of dealing fairly with their negro associates have few difficulties with the race problem. What one negro knows about them every negro in the community knows. The white people who in the negro's judgment have been unreasonable or unjust, he simply avoids. If he has to enter such employment, he endures it for only so long as is necessary and then departs as silently as the Arab. We have never encountered a negro who held to the belief that parting was a sweet sorrow. When dealing with the white man, the negro is frequently playing a part—the part which in his judgment is most pleasing to his white audience. If such entails smiles, laughter, rolling of the eyes in traditional negro manner, such antics are forthcoming. If he concludes that restraint best serves his purpose, then it becomes evident. He can be all things to all whites. The negro occupies an anomalous position in society. In regard to all the modern means of advancing himself he lags behind. This is due not only to his enforced inferior social level but also to his lack of knowledge of modern business methods. He lacks the ability to pursue objectives over long periods of time, and he is hampered by his ease of distraction. In a word, he is at a great disadvantage in this world which the white man has so cunningly molded to his own ends.

In other ways the negro is far ahead of his racial rival. For one thing he is far shrewder. He is more observant of his adversary. While we believe that the negro views the motives of his white associates with skepticism, this feeling does not destroy his interest in the objects of his emotion. This attitude is aptly shown by the manner in which he cajoles us into doing some of the things he wants us to do. While the issue is taking form he achieves a part at least of his purpose. Unknown to them the negro is constantly cozening his white associates and we believe enjoying it.

He shows his true feelings toward us by his reticences. Invariably he tells us just what he thinks would be good for us to know and no more. Though our negro servants have learned all the intimate news of the neighborhood long before we have become aware of anything of importance having happened, they impart this knowledge to us piecemeal. It is measured out to us in what they consider proper doses, as we break news to children. Strange to say, always this information which they convey to us with appraising eyes, turns out to be founded in fact. It is never exaggerated and many times has been toned down at its source in order that we

should not be shocked by the too sudden acquisition of knowledge. It would simplify our problem if we could theorize something after this fashion:

Certain diseases which are common among whites occur infrequently among negroes. This disparity is due to the habitual disregard which the negro displays toward all forms of disease. We may then assume that only those diseases tend to appear among the negroes which are impervious to human disregard—diseases against which emotional defenses are inadequate. If the white race employed the same emotional defenses, his history of disease incidence would parallel that of the negro.

While we believe that in the main this thesis is true, it is certainly not subject to proof in its entirety. Several disease patterns occur with great infrequency in the negro, but are common in the white race, concerning which up to the present at least, no psychogenic origin has ever been suggested. It may be that in spite of present difficulties this theory may be more fully proven; stranger things than this have happened in the field of medicine in the past two decades. What we believe at present, and we venture to say it is self-evident, is that the study of disease in the negro will advance rapidly all our knowledge of the psychogenic factors of disease as it occurs in both races.

The two cultural levels are so different that two entirely different taking-off places are afforded us in our comparative study. In time this opportunity will be lost to us. Already in certain communities where the two races mingle more freely than they do here in the South, the attitude of the negro toward disease is becoming like unto that of the white. Those who have read Frederick Steigmann's¹ analysis of gastric ulcer occurring in the two races at Cook County Hospital in Chicago, will recall the implied query as to why negroes must spend years in that city before they develop this disease. We must admit that this was no puzzle to us. It took the newcomer that period of time to have formed in his mind just what an ulcer was, and what it might portend. The rest was simple enough.

In time we in the South shall meet similar changes in our clientele. The primitive detached attitude toward disease and the naive courage of the negro are bound to fall before the type of knowledge that is being spread abroad. The radio and the printed pages of advertisements will play their part in the story. Through these two sources the American public derives the greater part of its medical knowledge and the negro is bound to be engulfed. We can reconcile our minds to that conclusion only by trying to believe that the present unfortunate state of the public knowledge in regard to all forms of sickness is merely a necessary step in our progress toward better things.

Much time and effort has been expended in discovering a genotypic form of disease which would distinguish such variations from

health as they appear in the two races. Little if any progress has been made in this direction. The reason is plain. Such efforts have confined themselves wholly to physical factors, and have disregarded the psychologic element in the problem. As we have already stated, there is no appreciable difference in the working of the physiology of the white body from that of the black. It would be opposed to all reason to expect such differences to appear out of a clear sky when the two races enter what we term a period of sickness. What has not been taken into account is the fact that each race carries on through its illnesses the same personality characteristics which distinguished it in health. That is true of the white man as it is true of the black man.

The latter type only concerns us in this study. If we would truly seek for a genotypic form of disease in the negro, then we must take the sum total of his personality, and not alone the physical workings as they are shown in his body. Whatever has been an element of strength remains with him when he takes to his bed. The same qualities of weakness which hampered his progress in his work-a-day life abide with him when he is under the care of his doctor. It cannot be too often repeated in this search for cause and effect in the instance of the sick negro that with him, as with all men, sickness is not a separate life into which he enters shutting all the doors of his past life behind him.

Nor a condition into which for some unknown cause he is born again with a novel but stereotyped personality. The period of the negro's sickness is nothing more than the progress of his previous life, with all its encumbrances whipped up to a greater speed by factors such as fever, delirium, malnutrition and all manner of physical urgencies. Viewed in this light, we have no difficulty in discerning a true genotypic form of disease in the negro. This form is not confined to any discrete infection, but molds and shapes the pattern of whatsoever type of disease the negro encounters.

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THE RELATIONSHIP OF ORTHOPEDIC SURGERY TO INTERNAL MEDICINE.*

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In its broadest concept, modern orthopedic surgery encompasses the problems of the skeletal structures and the mechanics of the

* Read before the Section of Orthopedic Surgery, New York Academy of Medicine, December 17, 1937.

viscera. Functional or organic involvement of these structures is of frequent occurrence in the daily routine of the general practitioner or internist, who has been trained to examine patients with a consciousness of the high incidence of orthopedic problems. It is decidedly less frequently observed by those who examine patients in the recumbent position or who fail to have patients strip further than the waist and whose inquiries do not include observations concerning posture, the mechanics of the lower back and feet, the shoe, the corset, the competency of the peripheral vascular system, the type of gait, occupational trauma, the type of chair or mattress commonly used.

The internist who recognizes the frequent occurrence of skeletal disturbance will summon the modern orthopedic surgeon with increasing frequency and satisfaction. The orthopedic surgeon who retains the broad viewpoint of the physician and is not afflicted with the shaft vision of the specialist will, with increasing frequency, recognize the advisability of summoning the internist to assist in the complications that so frequently either precede, accompany, or follow orthopedic conditions, most particularly those concerned with infection and metabolic derangement.

In private practice the approach to an ideal interrelationship seems more frequently fulfilled. Hospital practice is handicapped by the segregation of many of the orthopedic surgeons in orthopedic hospitals and in the general hospital by the lack of recognition of the vast importance of the orthopedic service. Your program this evening affords an opportunity for the interchange of ideas between orthopedic surgeon and internist.

Acute Arthritis. The patient with acute arthritis commonly consults the internist. In hospital practice such patients are usually admitted to the medical wards. All too frequently such patients are treated exclusively by the internist, whereas valuable information and assistance should be obtained from the orthopedic surgeon. In the acute arthritides characterized by effusion, aspiration of the joint is an invaluable diagnostic and therapeutic procedure. We internists are altogether too timid about this procedure which, if done by the orthopedic surgeon, should be wholly without risk. In the coccal infections (gonococcus, pneumococcus, streptococcus and staphylococcus), the diagnosis may remain in doubt until aspiration is performed. The laboratory findings may then indicate clearly the therapeutic regimen, both constitutionally and locally. In rheumatic fever the aspirated fluid is of negative diagnostic importance, but its removal often gives prompt and dramatic relief from pain and precludes the necessity of forcing the analgesics which will sooner or later disturb the digestive system and hence undermine the nutrition of the patient.

In acute arthritis the internist is prone to use rest, and either

inadequate or excessive immobilization. Inadequate immobilization results in excessive pain, where snug splinting, or the application of plaster or traction might give complete relief. Prolonged immobilization may result in deformity, stiffness, limitation of motion, atrophy, and even ankylosis.

With the possible exception of sulphanilamide, now under investigation, specific drug therapy has succeeded only in giving symptomatic relief. The tendency of all of the forms of salicylic acid to result in digestive disturbance, the fear that the derivatives of cinchophen may not only upset the digestion but cause varying degrees of damage to the liver cells, and the occasional toxic effect of amidopyrine upon bone marrow, impels the wise physician to utilize drugs as infrequently as possible. One might paraphrase the old axiom that he is the wisest physician who knows the greatest number of useless drugs.

Where the orthopedic surgeon has been first summoned to deal with the problem of acute arthritis, the responsibility must be shared with a competent internist. The latter must investigate the general condition of the patient, most particularly with regard to his cardiovascular status, and serve in a judicial rôle to interpret the reports and recommendations of the various interested specialists.

The present advances in the technique of artificial hyperpyrexia elevate the modern physio-therapist to a position where the orthopedist and internist, in close coöperation, may summon him with whole-hearted and hopeful expectation of a therapeutic result. The strenuous character of this therapy and the necessity of including care of the mechanics of the involved joint can be best accomplished by the close coöperation of physiotherapist, internist, and orthopedic surgeon.

The management of infectious arthritis is essentially in the hands of the internist. The search for the infective focus must be intensive. Abscessed teeth must be removed, infected tonsils must be enucleated, the nose and accessory cavities must not only be examined visually and radiographically, but a diagnostic lavage of the antra must be performed by an exceedingly competent laryngologist. In the absence of other findings the nasopharynx is to be scrutinized particularly for small pockets of pus in lymphoid tissue, as in the Thornwaldt abscess. The reproductive organs must also be investigated. This should include prostatic massage in the male and visual examination of the cervix in the female. The eradication of the infective focus should be performed promptly and as soon as the temperature approaches normal. There is no necessity for waiting weeks or months fearing to activate the lesion.

It is in infectious arthritis alone that I believe autogenous vaccines are of genuine value. The necessity of dealing vigorously with foci of infection is augmented by the fear that the infectious arthritis

may be a precursor of rheumatoid arthritis. Whilst many believe that the latter is an end-stage of the former, I am of the opinion that the two may be differentiated by the constitutional phenomena to be described later.

Of the metabolic acute arthritides, gout is the most frequently observed. It is my experience that the frequency of gout, including the gouty diathesis, is greatly underestimated. Where patients complain of any type of skeletal pain, including arthritis, peri-arthritis, synovitis, fibrositis, myositis, myalgia, or even recurrent phlebitis, a search for deposits of urates, a determination of the blood uric acid and, finally and most important, the therapeutic test should be initiated. In any instance where symptomatology is relieved by adequate dosage of a potent preparation of colchicum, by which I mean sufficient to cause diarrhea, the diagnosis of gout or gouty diathesis should be made. The more frequently the therapeutic test is done, the more frequently will the diagnosis be made. Such patients should be managed by the indicated dietetic principles, by maintenance doses of colchicum, and by the weekly or fortnightly exhibition of the time-honored calomel-saline sequence.

In acute traumatic arthritis, the tendency towards hemarthrosis and subsequent stiffness or ankylosis necessitates early consultation with the orthopedic surgeon for the purpose of aspiration and the early institution of motion. Persistent or repeated bleeding suggests the hemorrhagic diseases such as hemophilia or avitaminosis as in scurvy.

If traumatic arthritis is recurrent or if the trauma seems insufficient, investigation into the mechanics of the joint for a local etiologic factor should precede the discharge of the patient.

Chronic Arthritis. In dealing with chronic arthritis, the closest coöperation between internist and orthopedist is imperative. In the specific arthritides, such as syphilis and tuberculosis, the management is extraordinarily one-sided. For the most part, the luetic is under the care of the internist who must never neglect, particularly in tabes, to prevent deformity by adequate mechanical support and reëducational exercises. The patient with tuberculous arthritis is usually handled by the orthopedic surgeon who, at recurrent intervals, should insist on medical consultation, particularly directed to the detection of extension of infection in other parenchymal structures, to the presence of dissecting abscess or amyloidosis.

In the non-specific chronic arthritides, therapeutic chaos can only be prevented by the insistence, whether by the orthopedist or internist, on a preliminary survey by the various physicians concerned.

The necessity of differentiating between hypertrophic osteo-arthritis and rheumatoid or atrophic arthritis need not be stressed in this place. It is my opinion that hypertrophic osteo-arthritis and

spondylitis are essentially metabolic disorders. Trauma resulting from faulty mechanics is probably an important factor in the production and the continuance of symptoms. If uncorrected, it may lead to increased local or distant mechanical difficulty.

In hypertrophic osteo-arthritis, intelligent coöperation between orthopedist and internist should result in complete relief of symptoms almost without exception. The task of the internist is to reduce the weight of these patients, who are ordinarily obese, administer thyroid substance in dosage sufficient to raise to normal and maintain at normal the metabolic rate, inject potent estrogenic hormone at the climacteric, correct constipation and any other obvious metabolic abnormality. It is the function of the orthopedist by corrective exercises, the use of corsets, belts and other forms of mechanical aid, to coöperate with the internist in the therapeutic regimen. There are several practical points in the management of these patients which I wish to stress. The administration of thyroid must be checked by frequent estimations of the basal rate. It is essential, particularly for the orthopedic surgeon, to be certain that the rate is a basal rate and not merely a reading of oxygen consumption, performed under dubious circumstances by a technician. I have learned to look with grave distrust upon metabolic rate determinations as reported from commercial laboratories. The dosage of thyroid is a distinctly individual experiment. Any thyroid product put up by a reliable pharmaceutical house may be employed. It is the first task to raise the metabolic rate to normal and the dosage is the amount that is necessary in that particular individual to obtain the result desired. Certain patients will be exceedingly sensitive—others exceedingly refractory. *A priori*, I know of no way of distinguishing the two. In a rough way, 1 to 2 gr. daily may be the dosage for the patient whose rate varies between 0 and -10% ; 2 or 3 gr. between -10 and -15% ; and 3 to 5 gr. where the rate is below -15% . Having raised the basal metabolic rate to normal, the dose must then be reduced to a maintenance, for continuance of the corrective dosage will lead to toxic manifestations. Overzealous therapy may result in the production of toxic symptoms from the sudden change in tempo in patients whose basal rate is still on the minus side.

Another practical difficulty arises in the performance of corrective exercise. It is the greatest exception to find a conscientious patient who will do corrective exercises regularly without supervision. The cost of supervised corrective exercise today is far beyond the means of even the average patient. The physiotherapists who give corrective exercises rarely do good massage. It would seem to me worth while for you who are in active orthopedic practice to establish some central institution where corrective exercise and massage could be adequately performed for a moderate

fee. I am inclined to the belief that one of the reasons for the popularity of chiropractors and osteopaths is the failure of the medical profession to provide this type of service.

In patients with osteo-arthritis, it is my belief that no other procedure should be incorporated in the regimen unless the lesion is obvious, or the symptoms fail to respond to therapy, or if they recur despite therapy. I am opposed to the promiscuous extraction of teeth, or the enucleation of tonsils, or specific therapy directed to the sinuses, or the injection of protein or "specific" vaccines or drugs, or faddist diets, unless the indication is perfectly obvious and apparent, or the patient has failed to respond to the approach *via* mechanical measures and the correction of metabolic abnormalities. I would not oppose the removal of an obviously abscessed tooth or of tonsils which are grossly purulent, or which have been the site of peritonsillar abscess, or where there is a clear history of onset or exacerbation of the joint symptoms following tonsillar infection, nor would I oppose therapy directed to an obviously infected accessory nasal sinus; but I think it is incorrect and even reprehensible for dentists to advise and perform extractions with promise of relieving or curing arthritis, or for laryngologists to remove tonsils merely because the patient has joint pain, or for prostatic massage to be indulged in for that same reason. Vaccine therapy is of no value in this type of arthritis. Non-specific protein therapy may be of temporary value, but is probably not worth the pain and discomfort of administration. Physiotherapy by means of electrical apparatus, including short wave, is probably not worth the trouble or expense. The various faddist diets, such as the alkaline diet, low protein, low starch, low carbohydrate, or the so-called Hay diet (which separates proteins and carbohydrates), are all without scientific basis or practical result.

In classic rheumatoid arthritis, however, the point of approach is wholly different. Neither the etiology nor the pathogenesis of this discouraging and crippling disease seem adequately explained today by any of the theories or data available. While we can give the patient with hypertrophic osteo-arthritis every assurance that we can obtain a satisfactory therapeutic result, we are forced to confess that in the rheumatoid arthritides our prospect of significant accomplishment is in inverse ratio. The ominous spectre of the progressive deformity makes it imperative that the physician first consulted in rheumatoid arthritis obtain the closest coöperation of all available specialists and arrange a therapeutic problem that is immediately as inclusive as possible. Infected or even suspicious teeth should be extracted, the tonsils should be enucleated, the sinuses should be investigated, and not exonerated until diagnostic antral lavage is performed, cultures should be obtained from foci, vaccines should be prepared and administered, focal infection should

be sought for and eradicated in the genitourinary passages, and no stone left unturned by the specialist group in seeking and removing any possible causative agent. It is the function of the orthopedist, in the active stage of the disease, to prevent deformity and ankylosis by the earliest possible use of corrective mechanical devices, early massage and passive motion, and later to institute active motion and corrective exercises. The functions of the internist are manifold. The sufferers from this disease are typified anthropomorphically and psychologically. Ordinarily one deals with a patient who presents generalized visceroptosis, organ inferiority, and an autonomic imbalance with characteristic vasomotor instability. The resistance of these patients must be enhanced by the use of a high calorie diet rich in vitamins and the various organic elements. If there is any doubt about the absorption of the latter, the vitamins should be artificially administered by mouth or even parenterally, and augmented by the use of direct sunlight or ultraviolet radiation. Where, as so frequently occurs, secondary colitis develops, the absorption of the vitamin products and the minerals, particularly calcium and iron, may be insufficient; under which circumstance, transfusions and the injection of soluble preparations directly into the tissues must be practised. Whilst my experience is limited, I am inclined to believe that this dread colitis, which so commonly depletes the sufferer from rheumatoid arthritis, may possibly be prevented by the use of a tight abdominal binder opposing the distention and ptosis in the atonic bowel.

Though it may seem a far cry to you who are interested primarily in organic medicine, I am quite convinced of the important rôle of the psyche, both as an accessory etiologic factor in the onset of rheumatoid arthritis and as a potent factor in the course of the disease. Situational difficulties and internal conflicts attending the onset of the disease will usually be uncovered, if a sympathetic rapport exists between doctor and patient. The correction of the psychologic situation may prove to be an important factor in the management of the patient. In the course of the disease, with the protracted therapy, the disappointments and the remissions, the morale of the patient must be maintained. It is impossible to sustain nutrition or perform adequate corrective exercise in a disgruntled and disheartened individual. It is as necessary to splint the psyche as it is to use mechanical appliances on the troubled joint. The physician who neglects this aspect in therapy is doing a serious injustice both to patient and self.

How much is actually accomplished by specific therapy in rheumatoid arthritis, is, as yet, unknown. The disease tends to progress through remissions and exacerbations to an arrested phase. Usually the patient, and often times the observer, will be tempted to attribute any accompanying successful result to the concomitant therapeutic

measure. In all likelihood the meticulous protracted attention of the orthopedic surgeon and the equally undramatic, but sympathetic, general constitutional and psychologic care by the practitioner are the more potent, but less featured, therapeutic measures.

In the arrested stage of rheumatoid arthritis, the orthopedic surgeon comes into his great glory—for here, once the disease has been surely and certainly arrested, the alleviation of symptoms, the correction of deformity, and the rehabilitation of the patient by indicated procedures, either fusion or arthroplasty, rank amongst the great surgical triumphs of modern times. Equally superb is the extraordinary teamwork and technical skill that has been evolved by the orthopedic surgeon. Infection is no longer countenanced and operative reactions to prolonged and gigantic procedures are virtually negligible.

In rheumatoid arthritis, as in hypertrophic osteo-arthritis, drugs are used symptomatically. The coal tars may be employed liberally, provided they do not interfere with digestion. It is my invariable and infrangible rule never to use cinchophen or any of its derivatives, including atophan and tolysin, for I never again want to see any patient with degenerative hepatitis, whether or not the direct relationship between the cinchophen and the hepatitis has been scientifically proven. I do not believe iodides, either in organic or inorganic form, perform any function in the dissolution of the pathologic process, though I must confess that there are patients who report that they feel better when they take iodides, even though there is no evidence of syphilis. The value of sulphanilamide remains to be demonstrated. I have never seen any of the "miracle" drugs work, whether these were of domestic origin or imported from the Continent with the usual uncritical testimony that appears without adequate data in foreign medical journals controlled by their advertisers. There is no reason that pharmacologic substances readily absorbed by mouth or rectum should be given parenterally or intravenously, other than the desire of the injector, for whatever reason, to keep the patient in constant attendance. Except for symptomatic and psychologic relief, I do not believe that the physiotherapists have a significant contribution to make, and I know that the chiropractors and osteopaths constitute a genuine menace to patients in this category—state legislatures to the contrary, notwithstanding.

As to the status of climatotherapy in atrophic arthritis, it is doubtful whether the popular wave of enthusiasm is justified by the results. In advising climatotherapy, we may be merely running away from our problem. Its good results may be either the spontaneous remission of the disease or else a purely psychologic phenomenon resulting from the escape of the patient from the tension and the strain of urban life. Many sufferers from rheumatoid

arthritis present a pathetic spectacle. Arriving sans teeth, sans tonsils, sans hope and sans pocketbook, without an adequate preliminary survey, they wander from pillar to post, usually selecting that pillar or that post where the emptiest drum makes the loudest noise. It is small wonder that so many of them, discouraged and disconsolate, as the result of their medical mismanagement, either abandon hope and accept chronic invalidism and pathetic deformity, or else seek relief in the hands of the ever-present charlatans and fakers.

Postural Strain—Faulty Body Mechanics. Postural strain and faulty body mechanics account for a huge incidence of the skeletal symptoms encountered in every-day practice. The upright position, the violation of mechanical principles in the modern vogue as to shoeing, carriage, corsetting and sitting have given rise to a vast repertory of skeletal pains as the result of the abuse of the muscles, joints, and ligaments.

The pain in acute foot strain may be sufficiently severe to simulate claudication, and the spread from this mechanical derangement may be referred to the calf, thigh, or even the lower back. As a result of the lack of orthopedic consciousness in the mind of the practitioner, these widespread disturbances are treated as vascular disease, arthritis, muscular rheumatism, and every manner of therapy introduced except the simple and curative support. Nor is it sufficient for the therapist to be content with the simple relief of symptoms. To prevent recurrence and adequately manage these strains, the cause must be sought to determine whether this is a misuse of a normal structure, an occupational strain, or a compensatory derangement as the result of a shortened leg, or a tilted pelvis, a plantar wart, a painful bunion, ill-fitting shoes, incorrect seating, the strain resulting from a long-continued application of the foot to the gasoline pedal on a long motor trip, and so forth. Where there is doubt as to the diagnosis, the therapeutic test of firm strapping, with or without manipulation, by a competent orthopedic surgeon may settle the diagnosis far better than a multiplicity of laboratory, radiographic, and specialist examinations. In peripheral vascular disease, it is almost the rule that such patients will suffer mechanical strain. Even in the presence of diminished or absent oscillometer readings and all of the clinical phenomena of impoverished circulation, therapy directed to foot mechanics may give rise to striking relief of symptoms.

In the disabilities of the lower back, resulting from postural strain, it is almost the exception to find that the patient has received adequate orthopedic care unless all other methods of therapy have been exhausted. Obstetricians and gynecologists are all too prone to the belief that lower back pain results from gynecologic abnormalities in the uterus particularly. Many patients are subjected

to a surgical procedure under this misconception. The temporary relief that follows is the result of the rest in bed rather than the operative procedure, and the symptoms recur as soon as the upright position is resumed.

Even in the presence of marked hypertrophic osteo-arthritis, adequate postural treatment and the use of corsets, both in the male and female, may give prompt relief of symptoms despite marked radiographic evidence of bony involvement. Where lower back pain exists, the first thought should be toward the correction of postural strain and the orthopedic surgeon should be the first consultant rather than to have these patients run the gamut of a medical work-up and the unnecessary ministrings of dentist, laryngologist, physiotherapist, chiropractor, osteopath, or dietitian.

The diagnosis and treatment of acute back strain, with or without radiculitis, is oftentimes woefully mismanaged in general practice. Most often the severity of the symptoms misleads the practitioner to the belief that he is dealing with a nerve lesion, colic or embolization. Therapy, for the most part, is misguided and usually consists in the overliberal use of sedatives and narcotics; when an intelligent orthopedist, by the use of manipulation, traction, and mechanical therapy, by postural treatment, the use of a Bradford frame, or a plaster jacket, may give prompt and rapid relief without the exhibition of any of the powerful analgesics. When the presence of radiculitis, particularly of sciatic distribution, accompanies postural strain or hypertrophic osteo-arthritis, the diagnostic acumen is usually further impaired and therapy even more obviously misdirected. Under these circumstances the neurologist rather than the orthopedic surgeon is consulted. The cord is investigated, spinal fluid is obtained, epidural injections practised, usually without permanent relief and certainly without effect on the underlying postural strain. The patient, battered and weary, demoralized by overdosage with sedatives and narcotics, often resorts to the chiropractor or osteopath in sheer desperation. The cause for the failure of the practitioner to recognize abnormal body mechanics most often results from his method of examination. The hospitalized patient is seen in bed and rarely made to stand so that the mechanics may be observed. In private practice the patient is usually examined stripped to the waist so that it is only by chance that the lower extremities receive even a casual examination. Even under the optimum circumstances of medical practice in the wards of our most enlightened institutions, the most exhaustive notes on charts will be found and all manner of complicated laboratory examination with little or usually no comment concerning the body mechanics.

The transition from faulty body mechanics to traumatic arthritis, peri-arthritis, fibrositis, and the phenomenon of frozen joint, is by a gradation so slight as to be imperceptible. Probably no postural

strain occurs without some organic change in the skeletal structures. By whatever name one cares to designate the condition, one meets frequently with skeletal pain, whether in the shoulder, spine, lower back, or tarsus, in which the only demonstrable physical sign is interference with function and stiffness varying from the slightest degree up to and including almost complete ankylosis. Radiographic evidences of pathologic change may be minimal or absent. The patient is often relieved rapidly and dramatically by accidental trauma or purposeful manipulation which, in the later stages, must be performed under anesthesia. This syndrome is apparently unrelated to infection or metabolic disease, and will show no therapeutic response to any form of therapy other than manipulation. Until recent times manipulation has been neglected and even completely ignored by those of us in general practice. There is no doubt but that the consciousness of the orthopedic surgeon was aroused originally by the success of the bone-setters, the early manipulators, and more recently the chiropractors and the osteopaths. This latter group have undoubtedly performed their miraculous "cures" in individuals who have been misdiagnosed and mistreated by the practitioner or internist. As the result of the failure of the latter to recognize fibrositis, either the patient himself—disgusted with legitimate medical practice—seeks the chiropractor or the osteopath or, what is even more reprehensible, the practitioner refers the patient to the manipulator or else passively consents. Those of us who are in the general practice of internal medicine must be educated to the knowledge that the modern orthopedic surgeon includes manipulation in his therapeutic armamentarium, and is more competent, if less lusty, in his management of these mechanical conditions. If the internist or practitioner chides the orthopedic surgeon concerning the introduction of manipulation into his specialty, I would suggest that he be reminded that digitalis was introduced into medicine by the investigations of William Withering into the brew of an old herbalist.

It would be amiss to leave the discussion of lower back pain without mention of the organic phenomena which may be responsible and which include spondylolisthesis, herniation of the nucleus pulposus, metastases from carcinoma, and the fascial abnormalities that have been recently stressed by Ober. From personal experience alone I am of the opinion that many patients suffer from some type of dislocation of the vertebral structures, most likely involving the articular facets. Whichever of these mechanisms is operative, this type of skeletal distress will rarely, if ever, yield to the ministrings of the dentist, laryngologist, immunologist, urologist, physiotherapist, dietitian, or drug-therapist, and a result will not be obtained until the orthopedic surgeon is consulted.

In the diseases of the peripheral vascular system the necessity for

orthopedic consultation has been stressed elsewhere. The orthopedic surgeon, should he be first consulted by these patients, must insist upon the coöperation of the internist, particularly where there exists any of the metabolic abnormalities such as diabetes, or evidence of cardiovascular renal disease.

In the varicosities involving the lower extremity, there are times when pooling of the venous blood, shunting of the arterial blood and the resulting deficient oxygenation leads to cardiac dyspnea as in arteriovenous aneurysm. If this syndrome were more particularly sought, records of observations would be more complete.

Recurrent migrating phlebitis is a baffling problem upon which internist and orthopedist collaborate. I believe that local trauma to the foot, resulting from a combination of faulty shoeing or minor contusion or abrasion, in the presence of dermatophytosis is an important etiologic factor. This is recognized in lymphangitis and lymphadenitis of the lower extremity, and this mechanism may be an equally important factor in migratory phlebitis. Whether or not this is true, the therapy in migratory phlebitis should include elimination of the dermatophytosis and careful instruction as to the care of the feet. A second important etiologic factor in migratory phlebitis is gout and the gouty diathesis. Here the therapeutic test mentioned above is the best guide. Focal infection may play a dominant rôle in the pathogenesis, not only of phlebitis, but also of endarteritis.

In clinical medicine, skeletal abnormalities may give rise to symptoms that simulate underlying visceral disease. The scalenus syndrome may suggest peripheral vascular disease or cord tumor; slipping rib, as described by Eli Moschcowitz, may resemble cholelithiasis when right sided, particularly during the last months of pregnancy, and, when left sided, the anginal syndrome. The radiculitis accompanying cervical spondylitis may give rise to precordial pain of an anginal or pleuritic nature. Albuminuria resulting from a lumbar lordosis has resulted in the anxiety and discomfort associated with the prognosis and therapy of a serious nephropathy.

Mechanical disturbances of the internal viscera may justly be included in a survey of orthopedic surgery. Gastro-visceroptosis, particularly as a manifestation of a universal ptotic habitus, may give rise to the widest variety of symptoms simulating all types of organic or glandular disturbance. When full blown the syndrome exists in angular individuals who are underweight. Such patients appear almost cachectic, the complexion is muddy, there are rings under the eyes, the blood pressure is low and the basal metabolic rate is low, contrary to expectation. All complain of asthenia, and in the women there may exist amenorrhea and sterility. These patients suggest the syndrome of pituitary cachexia or Simmonds' disease, of which this is perhaps a *forme fruste*. It is from patients

of this type that the group of individuals with rheumatoid arthritis develop. Such patients usually visit the gastro-enterologists and dieto-therapists for high calorie feedings, the endocrinologists for substitution therapy, the gynecologists for manipulative or operative treatment for retroversion, retrocession, or sterility, until, in sheer disgust, they give up completely their quest for health. The intelligent coöperation of internist and orthopedist should obtain extraordinary relief for these patients. If they will consent to prolonged institutionalization and the time-honored Weir Mitchell rest cure with corrective exercises, particularly relative to costal breathing, they may frequently gain considerable weight with complete loss of their symptoms. Pregnancy is usually associated with a great sense of well-being, but may be followed by more striking asthenia and cachexia if a prolonged postpartum rest is not prescribed.

This presentation has been devoted to a cursory and sketchy summary of the problems common to clinician and orthopedic surgeon. Many of my happiest experiences in clinical practice have resulted from this inter-relationship. Your invitation to me tonight is indicative of your understanding and willingness to coöperate with those of us who practice internal medicine. I trust that this summary may serve to interest my own colleagues more intimately in the problems dealt with so competently by the orthopedic surgeons.

THE EFFECT OF PRONTOSIL AND RELATED COMPOUNDS UPON THE CHEMOTROPISM OF LEUKOCYTES.*

BY DALE REX COMAN, M.D.,
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(From the Department of Pathology, School of Medicine, University of Pennsylvania.)

SINCE the adoption of prontosil and related compounds as therapeutic agents, question has arisen as to their mode of action. Other than a slight retardation of growth, Colebrook and Kenny¹ found no evidence of bactericidal activity in their work with prontosil and streptococci. Nor were they able to demonstrate any "immune response" excited by the drug. Long and Bliss⁵ confirmed the results of Colebrook and Kenny in experiments *in vitro*, and from *in vivo* data were of the opinion that the results obtained in the treatment of infected mice could not be attributed entirely to a bacteriostatic action on the part of these substances. McKinney and Mellon⁶ concluded that their work was opposed to the conception of a direct action of the drug on the organisms.

* This investigation was aided by a grant from the Committee on Therapeutic Research of the Council on Pharmacy and Chemistry of the American Medical Association.

Since, then, it seems evident that the therapeutic action of these compounds does not depend upon the direct destruction of the organisms, other modes of activity must be supposed. The possibility of increased antibody formation might be considered, or accelerated activity of the reticulo-endothelial system, as suggested by the work of Davis, Harris and Schmeisser.² Another possibility that suggested itself was that these chemical agents might excite a strongly positive chemotropic response by the leukocytes and hence lead to increased phagocytic destruction of the organisms. The following experiments were undertaken to determine whether or not such an action could be demonstrated.

Method. Polymorphonuclear leukocytes were obtained by injecting physiologic saline solution into the peritoneal cavities of rabbits and withdrawing the fluid from 3 to 5 hours later. By lightly centrifugalizing this exudate and pouring off the supernatant fluid, a dense suspension of leukocytes was obtained. The cells were then suspended in plasma. The latter was procured by withdrawing 10 cc. of blood from the rabbit's heart and throwing the cells down rapidly in the centrifuge. The supernatant plasma was prevented from clotting by keeping the tubes packed in ice. A drop of the cell-plasma suspension was placed upon a coverslip and allowed to spread over a slide, upon which was the substance to be tested. In each instance this substance was placed upon the slide in the form of a tiny drop of less than 1 mm. in diameter and allowed to dry.

The directional movement of the leukocytes was then determined in relation to this drop of the test substance. The preparations were examined under the microscope at 37.5° C. and the paths of the leukocytes were charted by recording on paper their positions each minute for 10 minutes, through the use of a drawing ocular.

The measure of chemotropism adopted in these experiments was the number of micra per minute a cell moved toward, or away from, the test substance. This was computed by measuring the distance of the cell from the edge of the drop of test substance at the first and at the last observations. The difference between these two figures was divided by the number of minutes. The result was the number of microns per minute actually traversed by the cell toward, or away from, the test object. For example, if the position of a cell is 160 microns from the rim of the test object at the commencement of the observation period and 60 microns from it at the end of the 10-minute period, it has approached the substance a distance of 100 microns. This figure divided by the time (10 minutes) gives a chemotropic value of +10 microns per minute. A cell whose final position is more distant from the test substance than is its initial position has a negative value. In any experiment or group of experiments the result is expressed as the mean chemotropic value of all the leukocytes observed. The values obtained for strongly attracting substances, such as staphylococci, range from 10 to 15 microns per minute. Repelling substances give equally great negative values.

This method was used to test the chemotropic effects of prontosil, sulph-anilamide and setazine.

Experiments. In the first set of experiments prontosil soluble was used. This is the 2.5% red dye solution. It is the disodium salt of 4-sulphamido-phenyl 2'-azo, 7' acetylamino-1' hydroxynaphthalene-3'; 6' disulphonic acid. The preparation employed was that of Bayer ("Prontosil-Lösung, Bayer"). This solution was adsorbed

to finely powdered kaolin.* The kaolin was left in contact with the prontosil for 15 to 30 minutes. The kaolin particles were then thrown down in the centrifuge and a tiny drop of the resulting

TABLE 1.—CHEMOTROPIC EFFECT OF PRONTOSIL AND SETAZINE.

(Chemotropic effect of prontosil adsorbed on kaolin, carbon and hemolytic streptococci. No attraction of leukocytes is present. Setazine gives a slight attraction. The value in each instance is based upon 8 preparations.)

Test substances.	Mean value of chemotropism in microns per minute.
Prontosil on kaolin	-2.5
Kaolin control	-4.1
Prontosil on carbon	+0.1
Carbon control	+0.3
Prontosil on streptococci	+0.6
Streptococci control	+1.8
Setazine	+2.1

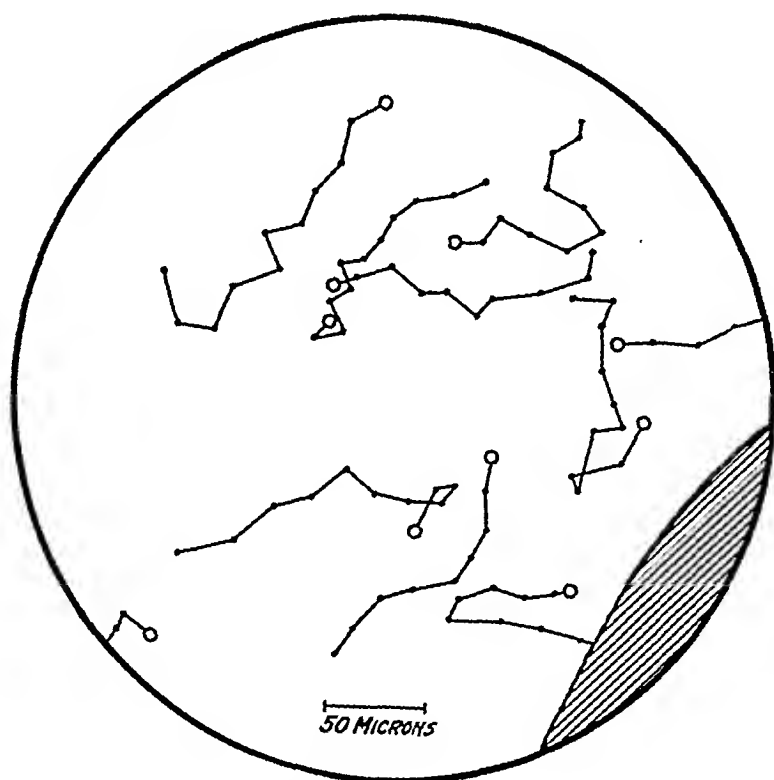


FIG. 1.—Camera lucida drawing of the paths of 10 leukocytes during a 10-minute period of observation. The shaded area represents part of a clump of hemolytic streptococci which had been treated with prontosil. The chemotropic value of this field is -0.6 micron per minute, *i. e.*, there was no attraction.

* It has previously been shown that kaolin is a satisfactory adsorbing agent for chemotropic substances.^{3,7}

heavy suspension was placed upon a slide and allowed to dry. The kaolin was stained pink by the prontosil and after the preparations were made, the dye was seen to diffuse slowly into the surrounding medium. A control drop of kaolin in double-distilled water was made upon the same slide a few millimeters away.

In 8 experiments with kaolin plus prontosil the mean value of chemotropism was -2.5 micra per minute based on 191 cells. In the control fields containing kaolin alone, the value was -4.1 micra per minute for 105 cells. The prontosil, then, had apparently slightly decreased the negative chemotropism of kaolin, by 1.6 micra per minute. To determine whether or not the difference between the control and test figures was significant the standard error was computed for each set of figures. The mean and standard error based on the 191 cells of the kaolin-prontosil fields is -2.5 ± 0.36 . The mean and standard error based on the 105 cells of the kaolin control fields is -4.1 ± 0.57 . The difference with its standard error is 1.6 ± 0.67 . Consequently there is a real difference between kaolin prontosil and the kaolin control, since the difference is more than twice its standard error; equal or greater differences would occur by chance only twice in 100 times.⁴ Hence prontosil, though it did not bring about positive chemotropism, did slightly decrease the negative chemotropic effect of kaolin.

Similar experiments were conducted with carbon particles as the adsorbing agent for the prontosil solution, using untreated carbon as the control. Eighty-two cells were examined in the carbon-prontosil fields and 76 cells in the carbon control fields. The cells in the carbon-prontosil fields gave a chemotropic value of 0.1 micron per minute toward the test substance. The control series gave a figure of 0.3 micron per minute toward the carbon. In other words, both control and test substances showed essentially indifferent movement of the cells. The standard errors were 0.53 and 0.71 respectively, and the difference between test and control values was found to be insignificant.

Though prontosil did not attract leukocytes, yet it seemed not unlikely that it would increase the chemotropic effect of streptococci when these were treated with the dye. Therefore in the next set of experiments, a strain of hemolytic streptococci, No. 1048, was employed. Preparations were made consisting of the streptococci from broth cultures, washed several times in double-distilled water. These organisms were allowed to remain in the 2.5% prontosil solution for periods varying from $\frac{1}{2}$ hour to overnight, after which they were washed once and then placed on the slide. The control on the same slide consisted of washed, but otherwise untreated, streptococci. The results are based on 8 experiments and a total of 97 leukocytes in the microscopic fields containing streptococci treated with prontosil, and 98 leukocytes in the control fields. The cells in the streptococci-prontosil fields showed a positive chemo-

tropic value of 0.6 micron per minute. The control cells moved 1.8 micron per minute toward the untreated streptococci. The standard errors were 0.68 and 0.52 respectively, and the difference between these figures was found to be insignificant by application of the statistical method referred to above.

In another group of experiments, preparations were made with sulphanilamide (Merck). Sulphanilamide is para-amino-benzene-sulphonamide. Crystals of this substance in double-distilled water were employed. In every instance, the leukocytes were apparently paralyzed by the concentration of the drug used. The cells failed to move in the neighborhood of the sulphanilamide crystals and would often appear to float in the plasma, suggesting a possible liquefaction of the plasma gel.

Similar preparations were made using setazine crystals. Setazine is the benzoyl derivative of sulphanilamide (Merck). Two hundred and seventy-six cells were followed in 8 preparations. It was found that the cells were attracted toward the setazine at a rate of 2.08 microns per minute. The standard error was 0.18. When compared to a mean of zero, the figure for setazine is significant, although in several of the preparations there was no attraction.

Summary. Experiments have been conducted using prontosil adsorbed on kaolin, carbon and streptococci in an attempt to determine the chemotropic effect of the drug for polymorphonuclear leukocytes. Leukocytes were obtained from the peritoneal cavity of the rabbit. Although the prontosil slightly reduced the negatively chemotropic effect of kaolin, it did not cause a positive chemotropic response. Adsorbed to carbon and to streptococci the prontosil did not alter the directional movement of the leukocytes in relation to the adsorbing agents. There is, then, no evidence from these experiments that prontosil attracts leukocytes.

Experiments in which sulphanilamide was used as the attracting substance showed that this substance, in the concentrations used, exerted a toxic effect upon the leukocytes which was expressed in a cessation of their movements.

Experiments using setazine as the source of attraction showed that this substance exerted only a weak attraction for the leukocytes and this was not constant.

It seems unlikely from these experiments that the therapeutic action of these drugs is due to an increased chemotropism of polymorphonuclear leukocytes.

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BOOK REVIEWS AND NOTICES.

A METHOD OF ANATOMY. Descriptive and Deductive. By J. C. BOILEAU GRANT, M.C., M.B., CH.B., F.R.C.S. (EDIN.), Professor of Anatomy in the University of Toronto. Pp. 650; 564 illustrations. Baltimore: William Wood & Co., 1937. Price, \$6.00.

UNDER the above title the author has produced a book on human anatomy designed chiefly for use by the medical or dental student in connection with dissection. The structures of the human body are described by regions rather than by systems and there are sporadic directions for the dissection of certain structures.

In his preface Grant states that his purpose is to present human anatomy in such a way that the student, by learning to correlate facts by studying them in their mutual relationships, will be led "inevitably to the apprehending of the underlying principles involved and the 'raison d'être' of such relationships. The student will thus learn to reason anatomically" And again he says: "The book is meant to be a working instrument designed to make Anatomy rational, interesting and of direct application to the problems of medicine and surgery."

Thus, instead of a conventional, systematic description, a running account of each region is given, in which he brings out rather strikingly, and with the aid of simple line drawings and explanatory diagrams (some of which are of the nature of animated cartoons), the principal features of the region, always attempting to correlate structure with function; and adding salient embryologic data, and brief clinical applications. Perhaps the most successful contributions consist in the bringing of ligaments to life, and in the interesting treatment of the joints, particularly of the hand and foot.

Following the lead of the latest edition of Cunningham, the nomenclature as revived by the British Anatomical Association (B.R.) is used. With Toldt's Atlas employing a special German Revision (N.K.) while all others except the British writers adhere to the internationally adopted B.N.A., the terminology appears to be reverting to chaos. Since there is a new international committee at work on a revision of the B.N.A. this outcropping of nationalistic nomenclature rebellion seems regrettable.

Just what place the book will find is difficult to predict. It is not complete enough to replace, for medical students, the systematic textbooks and atlases and is rather too extensive to be used generally as an addition to them. Possibly its most important mission will be to stimulate the established textbooks of anatomy to adopt a more functional standpoint, and to introduce more analytical and explanatory diagrams. It is a readable account of anatomy, and it brings out many anatomic facts in such an interesting and striking way that they seem to assume a new significance.

E. C.

MANUAL OF CLINICAL AND LABORATORY TECHNIC. By HIRAM B. WEISS, A.B., M.D., F.A.C.P., Associate Professor of Medicine, College of Medicine, University of Cincinnati, and RAPHAEL ISAACS, A.M., M.D., F.A.C.P., Associate Professor of Medicine; Assistant Director of the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan. Pp. 141. Philadelphia: W. B. Saunders Company, 1937. Price, \$1.50.

THE fifth edition of this manual has been revised to include several of the newer diagnostic procedures, especially in hematologic technique. The

volume compares favorably with similar technique manuals issued by the larger hospitals for their interns. It shares their advantages of covering much territory in a small compass and their disadvantages of being incomplete both as to subject matter and details of technique and interpretation. It includes, as formerly, sections on history taking and routine physical examination, on clinical laboratory technique, on technical ward procedures and tables of nutrition values. No attempt is made to cover the bacteriologic, serologic or chemical laboratory technique except for such procedures as might be carried out in an office practice. J. F.

LE TRAITEMENT DE LA TUBERCULOSE PULMONAIRE PAR LA TUBERCULINE.
By DR. M. JAQUEROD (LEYSIN). Pp. 43; 2 plates. Lausanne: Librairie Payot & Cie., 1937. Price, 2.50 Sw. fr.

THE author concludes from extensive clinical experience that tuberculin treatment, in properly selected patients, is an effective supplement to rest therapy and collapse measures. Repeated warning is given against the indiscriminate application of tuberculin. It should be rigidly restricted to the patient with chronic afebrile, torpid disease. However, about a quarter of all cases of tuberculosis are considered suitable. No extravagant claims are made, and the author's discussion is persuasive, although no experimental or statistical evidence is presented. The details of treatment are described in simple fashion in this volume.

H. I.

ARTIFICIAL FEVER. Produced by Physical Means; Its Development and Application. By CLARENCE A. NEYMANN, A.B., M.D., F.R.S.M., Associate Professor of Psychiatry, Northwestern University Medical School; Honorary Professor of Medicine, National University of Mexico, etc. Pp. 294; 68 illustrations and 21 tables. Springfield, Ill.: Charles C Thomas, 1937. Price, \$6.00.

DURING the past 10 years much work has been done on artificial fever produced by physical means. Dr. Neymann has compiled the results of this research in an interestingly written and welcome book. Important statements are italicized or printed in heavy type. The paper, printing, illustrations, charts and binding are very good. There are several minor typographical errors. The price is high for 300 pages.

The first 2 of the 15 chapters deal with basic theories, principles and the history of hyperpyrexia. The author points out that the production of artificial fever was not a haphazard affair, as several lay articles would have us believe, but was the result of the carefully thought-out researches of Neymann and Osborne. This fact is mentioned no less than six times in the first 100 pages.

The next 3 chapters deal with the physiology and technique of hyperpyrexia. Here the emphasis on rectal temperature control of the patient and many treatment details are valuable. Neymann is convinced that his method (electromagnetic induction) is the best, and he offers arguments for it and against the other means of producing fever. The book could be improved by a more complete and unbiased discussion of air-conditioned and infra-red cabinets.

The remainder of the book considers the treatment of individual diseases with artificial fever therapy. Separate chapters are allotted to Paresis, Tabes and Cerebrospinal Syphilis, Primary and Secondary Syphilis, Multiple Sclerosis, Chorea Minor, Arthritis, Gonorrhea, and Asthma. Each chapter contains brief historic and clinical discussions of the disease which

have a doubtful place and value. The technique for each condition is covered especially as to the range of temperature, duration and number of treatments. The author states clearly what may be expected of fever therapy. When other therapy is indicated, as in syphilis, Dr. Neymann strongly recommends it, but at times with insufficient detail. He frankly rates pyrexia as ineffective alone in early syphilis, a commendable conservatism. The chapter on gonorrhea is well written in spite of the author's limited experience of only 3 cases.

Throughout the work, a discursive and conversational style, anecdotal technique in case description, a disposition to generalize, often sweepingly on an experience or two and occasional loose statements about results, detract from the value of the work as a scientific contribution. Nonetheless overenthusiasm is avoided to the extent that non-fever methods get emphatic endorsement whenever applicable.

There is an excellent bibliography of 556 references. This book should be read by all physicians and technicians doing fever therapy work. It will give the general practitioner a survey of the indications, results to be expected and the limitations of hyperpyrexia, but he should not expect an unbiased discussion of the means of producing fever.

J. F.

HEART DISEASE IN GENERAL PRACTICE. By PAUL D. WHITE, A.B., M.D., Assistant Professor of Medicine, Harvard University Medical School. Edited by MORRIS FISHBEIN, M.D. Pp. 338; 45 figures. New York: National Medical Book Company, Inc., 1937.

In his preface the author states that he has compiled "a brief but practical and forceful summary of our present knowledge of the diagnosis, prognosis, and treatment of heart disease." The type of presentation throughout the main part of the book is that of questions and answers. In all, 152 questions are asked and answered. Sample questions are as follows: Is "indigestion" caused by heart disease? Of what value is blood pressure determination? Of what relative value are the so-called laboratory methods in cardiovascular examination? (the answer of this is given in percentage figures). May the "cardiac" child go to school?

In addition to the main part of the book, there is an appendix of 43 pages devoted to the proper handling of cardiovascular emergencies or "heart attacks."

There is undoubtedly a great need for books of this type, not only on heart disease but in practically every field of clinical medicine. The author is preëminently fitted for his task, not only by virtue of his comprehensive and accurate knowledge of the subject and his ability as a writer, but also his experience in giving courses for physicians. The less a practitioner who has to deal with heart disease knows about it, the more he needs this book. After he has learned the answers to the 152 questions, he will at least have a good start.

C. W.

BIOLOGICAL AND CLINICAL CHEMISTRY. By MATTHEW STEEL, Ph.D., Professor of Biochemistry in the Long Island College of Medicine, Brooklyn, N. Y. Pp. 770; 21 illustrations and 58 tables. Philadelphia: Lea & Febiger, 1937. Price, \$8.00.

In this book "the author has attempted to blend theoretical and practical biochemistry and biophysics with chemical pathology and clinico-chemical methods." The student is taught to use himself as a clinical subject, and perform on himself the many tests that are used in the modern study of the patient. Emphasis is laid upon the chemical separations that accompany

pathologic processes, rather than upon general biochemistry. A large number of experiments are detailed to illustrate the subject matter of the text. The book is readable and no doubt fulfills the purpose for which it is intended.

B. L.

JOURNAL OF NEUROPHYSIOLOGY (Issued Bi-monthly), Vol. I, No. 1, January, 1938. Editorial Board: J. G. DUSSEY DE BARENNE (Yale), J. F. FULTON (Yale), R. W. GERARD (Chicago), with an Advisory Board of 25. Pp. 85; illustrated. Springfield, Ill.: Charles C Thomas, 1938. Price, \$6.00 per volume.

THE first issue of this new journal contains 9 articles, 3 of which deal with peripheral nerve, 6 with cerebral cortex. They are concisely written and of enough importance to challenge the attention of readers following this field. It is only occasionally that a paper appears which fixes a conclusion in the memory with a clarity and force that promises permanence. The present Reviewer confesses that for him such experiences are rare; yet he has met two in this single issue: "Forced Circling Movements in Monkeys Following Lesions of the Frontal Lobes," by M. A. Kennard and L. Ectors, and "Functional Organization in the Sensory Cortex of the Monkey," by J. G. Dussey de Barcenne and W. S. McCulloch. The first number of this new journal justifies the editors in its inception and augurs well for its future.

G. McC.

CLAUDE BERNARD, PHYSIOLOGIST. By J. M. D. OLMSTED, Professor of Physiology, University of California. Pp. 272; illustrated. New York: Harper & Brothers, 1938. Price, \$4.00.

Claude Bernard, unquestionably one of the greatest pioneers in 19th century medical progress—Carrel's Foreword calls him "the father of modern medicine"—has received far less biographic attention in English than has his great contemporary and friend, Pasteur. Sir Michael Foster's out-of-print and not altogether sympathetic volume is, according to the author, the only book-length treatment of Bernard's life that exists in English, and even the French sources appear to be none too detailed or accurate. This volume, then, fills a conspicuous want and is especially welcome when written by an eminent physiologist whose interest of long standing has of recent years blossomed into painstaking, constructive first-hand study of the master physiologist. Many may not agree with him that "on a sufficiently broad view, Claude Bernard towers above Pasteur today as he did during his lifetime;" yet as one who more than any one else substituted the scientific method for empiricism in medicine, his importance is indeed incalculable. His enviable scientific method, and his emphasis on the value of experimentation are of almost equal importance. His concept of the "*milieu intérieur*" has only recently attained recognition as one of the most important basic principles of animal physiology; and his studies of pancreas and liver function properly place him as the father of modern endocrinology.

Like all great men, he had, of course, his weaknesses and made his mistakes. Possessing an ardent loyal personality, he was led by his master's (Magendie) incorrect observations of the complete absence of circulation in some cholera cases to a false theory of the lack of indispensability of the blood; his intense nationalism led him to claim for Frenchmen, including himself, discoveries that others attributed to English and German scientists; his numerous books, mostly from students' transcripts of his lectures, thereby necessarily contain repetitions, contradictions and inaccuracies. Curiously, his first book to be published from his lectures was in English, prepared by Walter F. Atlee, a young Philadelphia physician.

As well as making an excellent critical study of the great scientist, his methods and professional achievements, the author gives a lively picture of the man, his triumphs and his misfortunes, his foibles and his lovable qualities. Here the copious Raffalovich correspondence has been used to good effect. Next to Bernard's own unfinished "Introduction to the Study of Experimental Medicine," one can recommend the study of this volume as a means of getting to know more about one of the greatest figures in the history of modern medicine.

E. K.

PRACTICAL BACTERIOLOGY, HEMATOLOGY, AND ANIMAL PARASITOLOGY. By E. R. STITT, M.D., Sc.D., LL.D., Rear Admiral, Medical Corps, and Surgeon General, United States Navy, Retired; formerly Associate Professor of Medical Zoölogy, University of the Philippines; PAUL W. CLOUGH, M.D., Chief of Diagnostic Clinic, Johns Hopkins Hospital; Associate in Medicine, Johns Hopkins University, etc.; and MILDRED C. CLOUGH, M.D., formerly Fellow in Bacteriology and Instructor in Medicine, Johns Hopkins University. Pp. 961; 208 illustrations (4 in colors). Ninth edition, rewritten, revised and enlarged. Philadelphia: P. Blakiston's Son & Co., Inc., 1938. Price, \$7.00.

THE ninth edition of this well-known book is prepared in the usual excellent fashion. As compared to the eighth edition, the text is increased by 124 pages and all material gives evidence of extensive revision and rearrangement. Chapters on Rickettsia and Bartonella and on filterable viruses have been added to Part I, Bacteriology, and discussion of Spirochetes transferred to this section. To Part II, Hematology (Study of Blood, eighth edition), expanded from 67 to 95 pages, has been added 2 colored plates and 2 colored drawings from cases of leukemia and a chapter on Diseases of the Blood. Illustrations for the section on Animal Parasites, Part III, are improved. Part IV, Pathological Examination of various Fluid and Organs, is more than doubled in size. Chapters on Examination of Blood and Urine, and on Liver and Kidney Function have been included here rather than in the Appendix, and 2 new chapters, Endocrine Glands and Food Deficiency Disease, added. The authors and publishers are to be congratulated.

H. R.

DAS RHEUMABUCH DES DOCTOR BALLONIUS. Nach der Rheumasehrift des Lateinischen Textes. Gulielmi Ballonii, Liber de Rheumatismo et Pleuritide Dorsali, Paris, 1642. Deutsch Herausgegeben von Dr. WALTER RUHMANN, Spezialarzt für Innere Krankheiten in Berlin. Pp. 66. 1 illustration. Mittenwald: Arthur Nemayer, 1938. Price, Rm. 3.

THIS booklet, from a Press that seems to specialize on rheumatism, is chiefly concerned with rendering Guillaume de Baillou's book on rheumatism "aus der starren lateinischen Form in unser lebendiges Deutsch!" Doubtless for Germans the translated text is both more alive and clearer than to those for whom it is still in a foreign language. A short Anhang compares old and new rheumatism in an unenlightening manner: toxins, hormones and antibodies are correlated with the ancient doctrine of the humors, "shifts to the left" and "allergizing factors" hover about the effort to interpret the language of ancient medicine in terms of the combination of a new humoral pathology with Virchow's Cellular Pathology. To the author, for whom the study and treatment of disease are in a state of flux, Ballonius' work serves as an example of old knowledge attaining to new truths, though the Reviewer must confess that he cannot follow the sequence.

E. K.

THEORETICAL PRINCIPLES OF ROENTGEN THERAPY. Edited by ERNST A. POHLE, M.D., Ph.D., F.A.C.R., Professor of Radiology; Chairman, Department of Radiology and Physical Therapy, University of Wisconsin. Foreword by W. EDWARD CHAMBERLAIN, B.S., M.D., F.A.C.R., Professor of Radiology in the Temple University School of Medicine, Philadelphia. Pp. 271; 132 illustrations. Philadelphia: Lea & Febiger, 1938. Price, \$4.50.

THIS book presents the fundamental facts concerning Roentgen therapy in such a manner as may be easily assimilated by students of radiology even though they may not have a complete knowledge of physics. The entire book is compiled in such a way that one paragraph builds up the subject matter for subsequent paragraphs. The physical properties of the book such as the print and paper are of excellent quality.

The book deserves a place in every radiologic department. Any criticisms which are made of this text are minor. Since the book is a compilation of the work of different men, there is some tendency to overlap the subject matter. This does not detract from the quality of the book but rather aids in presenting more than one man's opinion of the same subject.

The chapters on dosimetry and protection from Roentgen ray are unusually practical and in themselves comprise a real asset to the library of any radiologist.

G. C.

THE PATIENT AND THE WEATHER. By WILLIAM F. PETERSEN, M.D. With the assistance of MARGARET E. MILLIKEN, S.M. Volume IV, Part 3, Organic Disease Surgical Problems. Pp. 651 (lithoprinted); 482 illustrations. Ann Arbor: Edwards Brothers, Inc., 1938. Price, \$10.00.

REGRET is expressed that the important work in this realm by investigators in continental Europe is comparatively unknown to English and American writers. This volume, the last but one of the series, is divided into 14 chapters, and the major subjects discussed are as follows: Infections and inflammation; ulcer of the stomach and duodenum, and Meckel's diverticulum; meteorologic environment and the gall-bladder attack; appendicitis; disturbances of the bowel; ectopic pregnancy; postoperative complications; vascular accidents; miscellaneous episodes; brain abscess; orthopedic cases; ophthalmologic episodes; glaucoma; epidemiology of the surgical cases; concluding chapter being a brief résumé.

The chapter on infection and inflammation is given most space, wherein the weather is stated to be a dominating factor in initiating the two major biologic rhythms—ARS and COD—and by their observance, the surgeon will be greatly aided. ARS phase shows anabolism and alkalosis, with increased blood pressure; there are reductive processes and contraction of smooth muscle fibers; hemorrhage and embolism are more apt to occur; spasm of sphincters and increased tension of scars; adhesions may tear and hollow viscera rupture; focal lesions become painful; drains may be expelled, sutures give way and herniotomy may occur(?). COD phase follows, with dilatation of arterioles, capillaries and venules, and blood pressure falls; oxidation and catabolism are enhanced; thrombosis and venous bleeding may occur; tissues swell, tension is increased and greater pain is experienced; muscle spasm and connective tissue spasm relax and healing is accelerated; temperature, pulse rate and metabolism are increased. Since many minor rhythms make up the major ones, the dividing line is not so sharp as the description may suggest.

With this volume, the study of the effect of environment upon organic disease is concluded. In the next, and final volume, "conception, morbidity, death and the relation of these to evolution," will be considered in a

more abstract form. This ponderous series, devoted to a much neglected subject, cannot be read lightly. The Reviewer again expresses the hope that the reader may be aided by the addition of an index to the concluding volume.
N. Y.

THE BIOLOGY OF ARTERIOSCLEROSIS. By M. C. WINTERNITZ, M.D., R.M. THOMAS, M.D., and P. M. Lecompte, M.D., The Department of Pathology, Yale University School of Medicine, New Haven. Pp. 142; 116 illustrations (many in color). Springfield, Ill.: Charles C Thomas, 1938. Price, \$4.00.

THOUGH diseases of the cardiovascular system head the causes of death, knowledge concerning their nature is still very incomplete. The causes of arteriosclerosis remain unknown, and the steps that lead to the development of the full-bloom state are obscure. The present monograph deals primarily with the interpretation of the structural changes in the diseased vessel wall; it represents an attempt to trace the processes to the inception and to follow them through their various stages. From this study there emerges a unified concept as to the nature of the sclerotic processes in the arteries, in the heart valves and in the veins.

In an age in which the latest method is often looked upon as the best, it is worthy of emphasis that the authors have made use of old tools and done so with striking success. They have employed clearing agents to render transparent whole vessel, and injection fluids to bring into view the vasa vasorum, and they have carefully dissected the cleared and injected vessels, coat by coat. By these means, now so greatly neglected, they were able to establish a better correlation between structures and lesions visible to the naked eye, and the subvisible; moreover preliminary study of the cleared and injected vessel has enabled them to select with ease and precision areas of particular interest for more detailed histologic investigation. One of the outstanding results of their study is the demonstration that an extensive vascular network of regular pattern ramifies throughout all the coats of the vessel wall. In response to various stimuli much proliferation of these vasa vasorum may take place, and some may attain considerable size. In the diseased artery, mural vascularity becomes greatly exaggerated.

The recognition that the walls of blood-vessels are richly vascular, forms the point of departure in the present investigation. The authors proceed to study the reactions of the vessel wall to injurious agents. They show that here, as in all other vascular tissue, exudation and proliferation occur as consequence of many types of injury, and that these reactions play a dominant part in the complex picture of arteriosclerosis. Of particular importance is hemorrhage from the vasa vasorum, for it may become very extensive, and lead to sudden occlusion of the lumen by rapid infiltration of the wall; or the leakage may be slow and less extensive and bring into activity processes that lead to removal of the escaped blood or to its organization, and to repair of the damaged wall. These are events of common occurrence and they, too, enter into the picture of the sclerotic processes. Intimately related to arteriosclerosis proper, is the mechanism of calcification, of atheromatous formation and of thrombosis, and these subjects are considered in the light of disturbed mural vascularity.

The authors did not find the causes of arteriosclerosis, nor did they furnish the solution of many of the multitudinous questions that arise when this disease is critically discussed. But they have added much of value to our knowledge, and their work marks a long forward step toward placing the problems of arteriosclerosis on a sounder basis. This monograph makes very stimulating reading, and clarifies the current, hazy, and ill-founded conceptions concerning arteriosclerosis.

Not the least valuable part of this thought-provoking book is the wealth of beautiful illustrations, many of their reproductions of photographs taken in natural colors. But a few years since, illustrations such as these would have placed the book beyond the pocket-book of most of us. At long last we have an American medical publication with an abundance of truly excellent colored illustrations published at a very moderate price.

B. L.

THE NEW INTERNATIONAL CLINICS. Vol. 1, New Series (Old 48), March, 1938. Edited by GEORGE MORRIS PIERSOL, M.D., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, Philadelphia. With 18 Collaborators. Pp. 322; illustrated. Philadelphia: J. B. Lippincott Co., 1938.

A NEW series of this distinguished periodical, now in its 189th volume, starts with this issue in a different and more attractive cover. Dr. Piersol's experienced leadership should go far in making the "Clinics" succeed, and all the more with the following distinguished list of American and foreign collaborators: F. G. Blake, R. L. Cecil, V. C. David, N. J. Eastman, K. M. Houser, W. J. Kerr, J. W. McNee, J. C. Meakins, G. R. Minot, J. W. Moore, J. H. Musser, L. J. Pollock, I. S. Ravdin, E. Rehn, B. S. Veeder, B. G. Wallace, R. M. Wilder, and A. C. Woods. International medicine, surgery, obstetrics and gynecology, pediatrics, neuro-psychiatry, ophthalmology, otolaryngology, and pharmacology are thus all represented by leaders of their specialties.

This number consists of 17 original contributions, 8 "clinics," and a review of recent contributions to biliary stasis and decompression, by A. Cantarow.

E. K.

THE TREATMENT OF CLINICAL AND LABORATORY DATA. An Introduction to Statistical Ideas and Methods for Medical and Dental Workers. By DONALD MAINLAND, M.B., CH.B., D.Sc. (EDIN.), Professor of Anatomy, Dalhousie University, Halifax, Nova Scotia. Pp. 340; 23 illustrations. London: Oliver and Boyd, 1938. Price, 15/-.

THIS book on statistical methods has several advantages over other works on the subject. These advantages are that it can be understood by every physician, it is actually readable and interesting, the problems may be worked by any one having a knowledge of arithmetic and elementary algebra, and most noteworthy, the examples are familiar to everyone practicing medicine. Thus the reader is shown exactly how to answer such questions as these: When is an increase from 70 to 80% of polymorphonuclears in a differential count significant, and when is it due to chance? To what extent are large samples of observations more reliable than small samples, and how large should samples be? What is the probability that two small series of blood pressure readings are significantly different? These are problems that nearly everyone meets, and consequently this book should be useful to a great many readers, especially to those who know nothing about statistical methods and perhaps distrust them.

The Reviewer suggests that when a second edition is brought out, it should include a few tables, so that it would not be necessary to refer the reader so often to other books containing tables. An example of how this may be done is given in Appendix III of H. L. Dunn's paper on "Statistical Methods in Physiology" (*Physiol. Rev.*, 9, 275, 1929); these tables may be profitably used by readers of Dr. Mainland's book.

M. McC.

ON THOUGHT IN MEDICINE (DAS DENKEN IN DER MEDIZIN). By HERMANN VON HELMHOLTZ. An address delivered August 2, 1877, on the Anniversary of the Foundation of the Institute for the Education of Army Surgeons. Introduction by ARNO B. LUCKHARDT. (Reprinted from Bulletin of the Institute of the History of Medicine, Vol. 6, No. 2, February, 1938). Pp. 27; 2 illustrations. Baltimore: The Johns Hopkins Press, 1938. Price, .75.

THIS reprint, consisting of a translation of Helmholtz' celebrated address, delivered in 1877 on the Anniversary of the Foundation of the Institute for the Education of Army Surgeons and a 3-page introduction by Arno B. Luckhardt, is a welcome addition to the output of the Hopkins Institute. Not a little of Helmholtz' address is as appropriate today as it was 60 years ago and probably will be 60 years from now. Perhaps we should be content that in some parts of the world *some* progress has been made in substituting observation, experiment and fact for theory and metaphysics.

E. K.

ON A NEW GLAND IN MAN AND SEVERAL MAMMALS (GLANDULÆ PARATHYREOIDEÆ). By IVAR SANDSTRÖM. [Upsala Läkareförenings Förhandlingar, 1879-80, 15, 441-471]. Translated by CARL M. SEIPEL, DR. MED. DENT. Edited by CHARLOTTE H. PETERS and J. F. FULTON. With biographical notes by PROF. J. AUGUST HAMMAR. Pp. 44; 1 illustration and 3 plates. Baltimore: The Johns Hopkins Press, 1938. Price, \$1.00.

THIS English translation is the only complete translation from the Swedish of the 30-page article by Sandström in 1880 which first described the parathyroid glands, which he had discovered when he was still a medical student. This is preceded by an interesting brief note on Sandström's life written by Hammar, an English abstract of Hammar's review on the parathyroids written in Swedish in 1908, and a translation of a letter from Sandström to his sister, which reveals his idealism in research. This is an attractive little book for those interested in looking back upon the important and dramatic steps in the development of medical knowledge.

I. Z.

ATHLETIC INJURIES. Prevention, Diagnosis and Treatment. By AUGUSTUS THORNDIKE, JR., M.D., Surgeon in the Department of Hygiene, Harvard University; Assistant in Surgery, Harvard Medical School, etc. Pp. 208; 104 illustrations. Philadelphia: Lea & Febiger, 1938. Price, \$3.00.

A MONOGRAPH of importance. Any school physician will benefit by reading the chapters on "Physical Fitness," "Physician Training," and "Physical Fatigue." The remainder of the book is a concise and valuable treatise upon the diagnosis and treatment of injuries sustained in sports.

G. W.

PNEUMONIA AND SERUM THERAPY. By FREDERICK T. LORD, M.D., Clinical Professor of Medicine, Emeritus, Harvard Medical School, etc., and RODERICK HEFFRON, M.D., Field Director, Pneumonia Study and Service, Massachusetts Department of Public Health, 1931-1935. Pp. 148; 10 figures and 10 tables. Revised edition of Lobar Pneumonia and Serum Therapy. New York: The Commonwealth Fund, 1938. Price, \$1.00.

THIS small volume is a revision of one published in 1936 under the title of "Lobar Pneumonia and Serum Therapy." Detailed information is included concerning the administration of the newer antipneumococcus

sera, both horse and rabbit. Reference is made to the results now beginning to appear from some of the State pneumonia control programs. To the general practitioner as well as the reader of more limited interests this little book should prove extremely useful.

L. C.

HERNIA. Anatomy, Etiology, Symptoms, Diagnosis, Differential Diagnosis, Prognosis, and the Operative and Injection Treatment. By LEIGH F. WATSON, M.D., Member of Attending Staff of California Lutheran Hospital and Methodist Hospital of Southern California, Los Angeles. Pp. 591; 281 illustrations. Second Edition. St. Louis: The C. V. Mosby Co., 1938. Price, \$7.50.

THIS second edition adds much of value for the reader. It, as does the first edition, presents the necessary features of anatomy, etiology, symptoms, signs, diagnosis, prognosis and mortality factors in the consideration of the care and treatment of this very common and important surgical condition.

The historic sketches are well done and extremely interesting, being more condensed and concise than in the first edition; also many of the older types of operations, proven impractical, have been omitted. Still too many are included for practical usage. The chapters on the medico-legal and compensation aspects of hernia have been thoroughly scrutinized and brought up to date. Several excellent chapters on the popular injection treatment are added. Comparisons between this and the operative treatment are made as to the complications, recurrences, expense, discomfort, mortality and time elements concerned.

The illustrations are very good on the whole and but few examples of monstrosities, instruments and the author's "pets" are included—a pleasing innovation. The new illustrations concerning the injection treatment are especially well done and useful.

The bibliography is very extensive, up to date and thorough, making this a real reference work.

There are, however, some minor adverse criticisms that must be noted. For example, the use of strychnia and such drugs for shock, mercurochrome for skin antisepsis, a different preoperative and postoperative skin preparation, inappropriate amount of space given to operative room technique—care of needles, sutures, dressings, etc. Added to these is the use of cocaine for local use, the objection to spinal anesthesia in the diabetic and the operative emptying of the proximal distended loop of gut in obstructed cases, on the basis of toxicity, this being responsible for reducing the mortality 25 to 50%.

Local anesthesia does not unfortunately answer the whole question of postoperative pulmonary complications as one infers from the author's statements.

With the exception of these few minor points the book is a very excellent one, well written, thorough, interesting, instructive and a valuable addition to any surgeon's library.

E. E.

DIGESTIVE TRACT PAIN. Diagnosis and Treatment. Experimental Observations. By CHESTER M. JONES, M.D., Assistant Professor of Medicine, Harvard University; Physician, Massachusetts General Hospital. Pp. 152; 5 figures and 1 plate. New York: The Macmillan Company, 1938. Price, \$2.50.

THE author states "It is the purpose of this little book to present a study on pain and other similar sensations caused by disturbances of the digestive tract." Admittedly abdominal pain is the major symptom upon which the clinician must depend for the accurate diagnosis of gastro-intestinal disease. The work is based upon both experimental data and clinical observations.

There are 8 chapters, a short bibliography and a very satisfactory index. The relation of the work of Ross, and Mackenzie and Head, to the observations of more recent investigators is discussed in a delightful introduction. There follows a most interesting chapter on "Heartburn." In regard to this symptom the author states "that these symptoms may be associated with actual regurgitation of stomach contents, which at times reach the mouth, is not to be doubted, but that the character of the regurgitated fluid has much, if anything, to do with the cause of the symptom is open to very grave doubts. There then follows in sequence a description of the reference of pain from the entire gastro-intestinal tract after which is a chapter on the "Clinical Application of the Experimental Observations." Many clinical protocols are included in the remaining portion of the volume. These in fact take up more than one-half of the volume. A unique feature is the chapter on "Gastro-intestinal Pain in Functional Disease." Every practitioner of experience realizes the necessity of considering the psychogenic aspects of patients with functional disease. This little volume is simply and well written so that it makes easy reading. It is a worthy addition to the Macmillan Medical Monographs. I. R.

SOME ACCOUNT OF THE PENNSYLVANIA HOSPITAL. From its First Rise to the Beginning of the Year 1938. By FRANCIS R. PACKARD, M.D. Pp. 133; illustrated. Philadelphia: Printed by the Engle Press for the Pennsylvania Hospital, 1938. Price, \$2.50. (Books are obtainable from the Pennsylvania Hospital, 8th and Spruce Sts., Philadelphia.)

THE Pennsylvania Hospital, in its long history as the oldest independent hospital for the care of the sick in this country, has been singularly fortunate in its historians. Following Benjamin Franklin's "Some Account," printed by him in 1754, we have Malin's short account in 1831, George B. Wood's history of the first century (1851), J. Forsyth Meigs' history of the next 25 years (1876) and Thomas G. Morton's extremely detailed account of 1895. Its very completeness, however, militates against the readability of Morton's history, so that lovers of the Hospital would now for some years have welcomed a brief account that would again bring its history up to date in pleasant form for the general reader. For this task none could have been better fitted than the present author—a medical historian of note, with a charming style, and long steeped in the traditions of the Hospital that he has served so long and well. He certainly has achieved his purpose of presenting "in as nearly as possible narrative form a brief account of the chief points of interest" of the institution.

Beginning with a brief account of the hospital's memorable foundation, the narrative recalls to us the colonial atmosphere of its early years, the early buildings, Franklin's incomparable cornerstone inscription, early expedients for raising money, the "elaboratory," the sunstroke tent and similar vivid pictures. Medical teaching, the Pathological Museum and Laboratory, the Out Patient Department, the Training School for Nurses, the Department for Mental and Nervous Diseases, and the Pennsylvania Hospital Unit in the World War, all have their high points of interest presented. There is no index, nor is one to be desired in a narrative that does not aim at reference use. The list of official prints of the Hospital, however, is an innovation of distinct reference value.

The typography (Caslon) and format of Franklin's "Account" has been copied to good effect. The illustrations, which are well chosen and reproduced, constitute an especially pleasant feature for those acquainted with the Hospital: rare portraits of the first staff, some of the Fothergill plates, hospital views, pleasant little drawings of hospital nooks and memorabilia by F. deP. Rothermal and photographs by E. F. Forney, all add to the attractiveness of a book that will be prized by the Hospital's many friends and appreciated by an even wider circle. E. K.

NEW BOOKS.

Practical Otolology, Rhinology, and Laryngology. By ADAM EDWARD SCHLANSER, M.D., Colonel, Medical Corps, United States Army; Chief of the Eye, Ear, Nose and Throat Service, Letterman General Hospital, San Francisco, etc. Pp. 315; 81 illustrations. Philadelphia: Lea & Febiger, 1938. Price, \$4.50.

Methods of Tissue Culture. By RAYMOND C. PARKER, Ph.D., Associate in Experimental Surgery, The Rockefeller Institute for Medical Research, New York. With a Foreword by ALEXIS CARREL, M.D. Pp. 292; 109 illustrations. New York: Paul B. Hoeber, Inc., 1938. Price, \$5.00.

The Medical Clinics of North America, Vol. 22, No. 3 (Boston Number, May, 1938). Pp. 322; 11 illustrations. Philadelphia: W. B. Saunders Company, 1938.

The Symposium in this Boston number includes 11 articles on various aspects of nervous and mental diseases. There are 13 other presentations covering a wide range of medicine. The Cumulative Index, which includes all articles published in 1938, gives both page and month of appearance.

Cause and Prevention of Disease. By WILLIAM HARVEY PERKINS, M.D., Professor and Director of the Department of Preventive Medicine and Director of the Hutchinson Memorial Clinic, The Tulane University of Louisiana, New Orleans, etc. Pp. 713. Philadelphia: Lea & Febiger, 1938. Price, \$7.50.

Embryonic Development and Induction. By HANS SPEMANN, Professor Emeritus of Zoölogy, University of Freiburg im Breisgau. Pp. 401; 192 illustrations. New Haven: Yale University Press, 1938. Price, \$5.00.

The Biology of Arteriosclerosis. By M. C. WINTERITZ, M.D., R. M. THOMAS, M.D., and P. M. Lecompte, M.D., The Department of Pathology, Yale University School of Medicine, New Haven. Pp. 142; 116 illustrations (many in color). Springfield, Ill.: Charles C Thomas, 1938. Price, \$4.00. (Review, p. 284.)

Life, Heat, and Altitude. Physiological Effects of Hot Climates and Great Heights. By DAVID BRUCE DILL, Fatigue Laboratory, Harvard University. Pp. 211; 25 illustrations. Cambridge: Harvard University Press, 1938. Price, \$2.50.

Handbook of Hematology. In four volumes. Vol. 1. Blood Cells, Leucocyte Function, Blood Platelets, Megacaryocytes, Hemorrhagic Diatheses, Supravital Staining; pp. 1-698. Vol. II. Comparative Hematology, Embryogenesis, Blood of Infants, Reticulo-endothelial System, Monocytic Leucemia, Fibroblasts, Histocytes, Lymphatic Organs, Tissue Cultures; pp. 699-1586. Vol. III. Spleen, Hemolymph Nodes, Bone Marrow, Myeloid Metaplasia, Anemias, Hemolytic Jaundice; pp. 1587-2360. Vol. IV. Polycythemia, Hemoglobin, Metabolism, Infectious Diseases, Benzol, X-Rays, Radium, Agranulocytosis, Leucocytosis, Leucemia, Lymphosarcoma, Leucosarcoma, Index; pp. 2361-3136. Edited by HAL DOWNEY, University of Minnesota Medical School, Minneapolis. Contributors: WILLIAM BLOOM, C. H. BUNTING, R. S. CUNNINGHAM, ISRAEL DAVIDSOHN, C. A. DOAN, HAL DOWNEY, MADELEINE FALLON, B. E. HALL, G. A. HARROP, F. J. HECK, G. M. HIGGINS, RAPHAEL ISAACS, R. H. JAFFÉ, O. P. JONES, H. E. JORDAN, H. W. JOSEPHS, PAUL KLEMPERER, F. J. LANG, W. P. LUCAS, F. C. MANN, V. R. MASON, S. R. METTIER, E. MEULENGRACHT, N. A. MICHELS, F. R. MILLER, E. E. OSGOOD, M. N. RICHTER, A. R. RINGOEN, NATHAN ROSENTHAL, F. R. SABIN, LAURENCE SELLING, C. C. STURGIS, E. H. TOMPKINS, C. J. WATSON, C. V. WELER, M. M. WINTROBE, MARTHA WOLLSTEIN. Illustrations, 1448, including 50 colored plates. New York: Paul B. Hoeber, Inc., 1938. Price, \$85.00 the set.

Play and Mental Health. By JOHN EISELE DAVIS, M.A., Veterans' Administration Facility, Perry Point, Md. Pp. 202. New York: A. S. Barnes & Co., 1938. Price, \$2.50.

A Symposium on Cancer. Addresses by LEIV KREYBERG, CLARENCE C. LITTLE, MADGE T. MACKLIN, EDGAR ALLEN, HOWARD B. ANDERVOUT, JAMES EWING, GIOACCHINO FAILLA, HENRI COUTARD, WARREN H. LEWIS, STANLEY P. REIMANN, JAMES B. MURPHY, and EMIL NOVAK. Given at an Institute on Cancer Conducted by the Medical School of the University of Wisconsin. Pp. 202; illustrated. Madison: The University of Wisconsin Press, 1938. Price, \$3.00.

The New International Clinics. Vol. 2, N. S. 1 (Old 48th), June, 1938. Edited by GEORGE MORRIS PIERSOL, M.D., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, Philadelphia. With 18 Collaborators. Pp. 315; illustrated and 1 colored plate. Philadelphia: J. B. Lippincott Company, 1938.

Baron Constantin von Economa. His Life and Work. By his wife and by PROF. J. VON WAGNER-JAUREGG. Translated from the second German edition by RAMSAY SPILLMAN, M.D. Pp. 126; illustration. Burlington, Vt.: Free Press Interstate Printing Corp., 1937. Price, \$2.00.

Data on the Growth of Public School Children. (From the Materials of the Harvard Growth Study.) By WALTER F. DEARBORN, Professor of Education and Director of the Psycho-Educational Clinic, Graduate School of Education, Harvard University, JOHN W. M. ROTHNEY, Instructor in Education and Research Associate at the Psycho-Educational Clinic, Graduate School of Education, Harvard University, and FRANK K. SHUTTLEWORTH, Assistant Professor of Education, Department of Education, and Research Associate, Institute of Human Relations, Yale University. Vol. III, No. 1 (Serial No. 14). Pp. 136. Price, \$1.00.

A Handbook of Methods for the Study of Adolescent Children. By WILLIAM WALTER GREULICH, Ph.D., HARRY G. DAY, Sc.D., SANDER E. LACHMAN, M.D., JOHN B. WOLFE, Ph.D., FRANK K. SHUTTLEWORTH, Ph.D. Vol. III, No. 2 (Serial No. 15). Pp. 406; 30 illustrations. Price, \$2.25.

The Adolescent Period. A Graphic and Pictorial Atlas. By FRANK K. SHUTTLEWORTH, Institute of Human Relations, Yale University. Vol. III, No. 3 (Serial No. 16). Pp. 246; 458 illustrations. Price, \$2.00. Monographs of the Society for Research in Child Development. Washington, D. C.: Society for Research in Child Development, National Research Council, 1938.

The Culture of Organs. By ALEXIS CARREL and CHARLES A. LINDBERGH. Pp. 221; 110 illustrations (38 plates). New York: Paul B. Hoeber, Inc., 1938. Price, \$4.50.

The Life of Chevalier Jackson. An Autobiography. Pp. 229; many illustrations, some in color. New York: The Macmillan Company, 1938. Price, \$3.50.

A Synopsis of the Diagnosis of the Acute Surgical Diseases of the Abdomen. By JOHN A. HARDY, B.Sc., M.D., F.A.C.S., El Paso, Texas. Pp. 345; 92 illustrations. St. Louis: The C. V. Mosby Company, 1938. Price, \$4.50.

The International Medical Annual. A Year Book of Treatment and Practitioner's Index. Fifty-sixth Year, 1938. Editors: H. LETHBRY TIDY, M.A., M.D. (Oxon.), F.R.C.P., and A. RENDLE SHORT, M.D., B.S., B.Sc., F.R.C.S. Thirty-five Contributors. Pp. 615; 103 illustrations and 68 plates. Baltimore: William Wood & Co., 1938. Price, \$6.00.

This well established annual—now in its 56th year—continues to be a good distillation of the year's medical progress. From "Abdominal Surgery" to "Yoga—a Medical Study" the field is well covered by eminent British contributors and "everyword is new."

The Special Pathological Anatomy and Pathogenesis of the Circulatory, Respiratory, Renal and Digestive Systems Including the Liver, Pancreas and Peritoneum. By HORST OERTEL, Strathcona Professor of Pathology, Director of the Pathological Institute, McGill University, and Pathologist-in-Chief to the Royal Victoria Hospital, Montreal, Canada. Pp. 640. Montreal: Renouf Publishing Company, 1938. Price, \$8.50 from T. H. McKenna Inc., 878 Lexington Ave., New York City.

The Chemistry of the Sterids. By HARRY SOBOTKA, Chemist to the Mount Sinai Hospital, New York. Pp. 634. Baltimore: The Williams & Wilkins Company, 1938. Price, \$8.50.

The Pituitary Gland. An Investigation of the Most Recent Advances. The Proceedings of the Association, New York, December 28th and 29th, 1936. (Association for Research in Nervous and Mental Disease, Vol. XVII of a Series of Research Publications.) Editorial Board: WALTER TIMME, ANGUS M. FRANTZ and CLARENCE C. HARE. Pp. 764; 160 illustrations, 6 plates and 53 tables. Baltimore: The Williams & Wilkins Company, 1938. Price, \$10.00.

Pavlov and His School. The Theory of Conditioned Reflexes. By PROFESSOR Y. P. FROLOV, M.D., Member of the All Union Institute of Experimental Medicine, Moscow. Pp. 291; 27 illustrations. New York: Oxford University Press, 1937. Price, \$4.00.

Maternal Care Complications. The Principles of Management of Some Serious Complications Arising During the Antepartum, Intrapartum, and Postpartum Periods. Approved by The American Committee on Maternal Welfare, Inc. Prepared by R. D. MUSSEY, M.D., P. F. WILLIAMS, M.D., and F. H. FALLS, M.D. F. L. ADAIR, M.D., Editor. Pp. 95. Chicago: The University of Chicago Press, 1938. Price, \$1.00.

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PROGRESS OF MEDICAL SCIENCE

SURGERY.

UNDER THE CHARGE OF
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FRACTURES OF THE NECK OF THE FEMUR.

FRACTURES of the neck of the femur have long constituted a serious problem, not only as regards prognosis for restoration of function but for life as well. This fracture, most commonly occurring in the aged has been for many an old individual the unpleasant incident which ushered in a train of factors to terminate life. Long periods of immobilization of the fracture site prove in instances more dangerous than the fracture itself, so that frequently the fracture has been ignored in the hope that death from pneumonia, exhaustion, or decubitus ulcers with associated infection might be prevented.

The following quotation from Smith^{44a} in 1854 illustrates the lugubrious viewpoint of his time, a viewpoint which has not been changed universally in our own time:

"Our prognosis in cases of fracture of the neck of the femur must always be unfavorable; in many instances the injury soon proves fatal, and in all the functions of the limb are forever impaired; no matter whether the fracture has taken place within or external to the capsule, whether it has united by ligament or bone, shortening of the limb and lameness are the inevitable results. In forming our prognosis, we must take into account principally the age of the patient, and the situation and nature of the fracture. The results of my own experience would lead me to say, that the form of fracture which is most rapidly and most frequently fatal, is the extra-capsular fracture, when it is accompanied by a comminuted fracture with displacement of the trochanters;

but as regards the functions and utility of the limb during the remainder of the patient's life, the intra-capsular fracture is the more serious accident, for, independent of the difference which exists between these two varieties of the fracture, as regards the possibility of osseous union, there is likewise a remarkable difference with respect to the ultimate shortening of the limb; for in the extra-capsular fracture the amount of shortening which took place when the injury occurred seldom subsequently undergoes any very material increase, but when the fracture is seated within the capsule, absorption of the neck of the bone slowly but steadily proceeds, and an amount of shortening of the limb is thus ultimately produced, equal to, or, in many cases, even greater than the entire length of the neck of the femur.

"In fatal cases death may be owing to a variety of causes: sometimes the patient dies in a few days from the effects of the shock upon a system already enfeebled by age; very frequently bronchitis sets in, and terminates fatally before ten days have elapsed; in other cases the accident is followed by a severe irritative fever, the tongue becomes furred, the bowels constipated, the pulse quick and feeble, and the patient restless and thirsty; he is unable to sleep, and complains much of the pain about the joint; the tongue soon becomes more loaded, the countenance dejected, and expressive of distress and anxiety; the patient begins to talk incoherently, and raves at night, then the pulse fails, the tongue becomes dry and brown, sordes collect about the lips and teeth, the anxiety of countenance and restlessness increase, the bronchial tubes become filled with mucus, a tendency to stupor, or coma, manifests itself, and then death terminates the scene. This form of fever is especially apt to be induced when the injured limb is kept firmly secured in splints and bandages, and maintained in a state of forcible extension."

Likewise Malgaigne³³ (1859) expresses the viewpoint of the day with regard to fracture of the neck of the femur:

"The prognosis is always grave; with very rare exceptions, a patient with intra-capsular fracture will be maimed for life, and sometimes even lose the use of the limb entirely. There is besides at the outset a still greater danger to be warded off. . . . The ancient school, still represented by Boyer, held that the want of union in these fractures depended solely on want of contact and of sufficient apparatus; whence they attached great importance to reduction, and contrived a variety of plans for making permanent extension.

"Another school, with Sir Astley Cooper at the head, regarding consolidation as impossible in the immense majority of cases, abandoned all attempts at reduction and all forms of apparatus. 'I should,' says Sir Astley, 'if I sustained this accident in my own person, direct that a pillow should be placed under the limb throughout its length, that another should be rolled up under the knee, and that the limb should be thus extended for ten days or a fortnight, until the inflammation and pain had subsided. I should then daily rise and sit in a high chair, in order to prevent a degree of flexion which would be painful; and walking with crutches, bear gently on the foot at first; then gradually more and more, until the ligament became thickened, and the muscles increased in their power. A high-heeled shoe should be next employed, by which the halt would be much diminished.'"

It might be argued that this is an ancient view of the prognosis and treatment of fractures of the neck of the femur. Several authors in the twentieth century have indicated the futility of treatment of this fracture, not only by intimation but by direct statement. In present day texts the note of futility is to be found. Homans¹⁸ indicates that it is frequently necessary to disregard the fracture and to look after saving the life of the patient. Stimson⁴⁸ states that in old people "an ideal anatomic restoration of form is impossible and the surgeon must be content to get union with a shortened neck and probably with changes in the angle which it makes with a shaft." Babcock² states that in the aged, death occurs in 17% from intercurrent affections, and bony or firm fibrous union is rather unusual. Ashhurst¹ is hardly more optimistic when he states that 1 out of 5 die in the first year after the injury and in those who recover, a useful limb results in about 7% of cases; nearly all of these have a limp and slight eversion.

Fortunately, the outlook exemplified by the quotation from Sir Astley Cooper is not borne out by the best available statistics of the past 15 years. The work of Royal Whitman⁵² brought new hope to the problem, when he showed that it was possible to obtain and maintain reduction of the fragments in intracapsular fractures of the femur. Presented in 1897, Whitman's method of treating fractures of the neck of the femur has been utilized with varying degrees of success. One great deterrent to treatment has been the influence of Sir Astley Cooper⁹ who felt that bony union could not take place in fractures of the neck of the femur.

Smith⁴⁶ has written: "In the third volume of Guy's Hospital reports (New Series), there is a paper by Mr. Bransby Cooper upon the causes of the non-union of these fractures, in which he dwells at some length upon the evil which he supposes would result, if osseous union were to occur: he remarks, 'What would have been the result if such union were admitted? That the provisional callus itself would have filled up the acetabulum, and in every way have so interfered with the structure of the joint as in itself to have proved destructive to the performance of every natural function of the limb. My object has been throughout to maintain, that it is ordained by nature that fracture of the neck of the femur, within the capsular ligament, is not to unite by ossific deposition.'"

Smith, however, felt that this opinion was an error and stated that "whenever reparation by bone occurs in the intracapsular fracture, it is owing to the direct union of the broken surfaces and that the effusion of callus around the fragments is by no means essential to the process."

That bony union can and does occur is not now contested. However, for the likelihood of success of union it is necessary for the fragments to be in apposition. Lack of approximation probably accounts for the large number of cases in which non-union results. Whitman has shown that it is possible to obtain approximation and maintain it by abduction technique. Those who have had best results with the Whitman method have adhered to fundamental principles of fracture care, namely, proper adequate reduction, and immobilization. For proper reduction, a general anesthetic is usually necessary. In an elderly patient this is often feared, but as has been pointed out by many, the dangers from a short general anesthesia should be less than the consequences of dis-

comfort from a poorly reduced fracture. For success with the Whitman method, not only must reduction be obtained, but in order to maintain the reduction it is necessary that the extremity be truly abducted on the pelvis. Tilting of the pelvis may at times simulate true abduction.

Löfberg²⁰ studied a series of 139 cases of intracapsular fractures over the period 1909 to 1922 who were treated by the abduction method. He did not mention the work of Whitman, but his method was similar in detail to the Whitman technique except for the addition of impaction as suggested by Cotton.¹⁰ The study is presented in great detail so that there is little difficulty tracing the results in individual cases. Of the 139 cases, 83 had satisfactory results in that function was restored. In 61 (almost half of the cases) there was complete restoration with no subjective symptoms. Eight cases died as a result of their injury, a mortality of 5.7%. The results recorded by Löfberg, 67% return of function, while not so good as might be hoped for, is much better than might be expected on account of the age of most of these patients. Other authors^{6,16b,40,47} have likewise reported a high incidence of good results by use of the Whitman method, but this degree of success is neither universal nor usual. Henderson,^{16a} as a result of experience with cases previously treated by others, concludes that the cause for many poor end results is due to improper diagnosis and treatment.

Non-operative methods for treatment of intracapsular fractures of the hip have in common one principle, reduction of the fracture and fixation in abduction and internal rotation. Whether the fixation is by means of plaster as in the cases treated by Whitman and others⁴⁰ or by traction,^{5,19,34,38,43} good results depend on the ability to hold the fragments of the fractured neck of the femur in apposition by abduction and internal rotation after adequate reduction.

Difficulties associated with the maintenance of reduction have brought about many attempts at fixing the fragments together by operative means. In 1878, Trendelenburg¹³ sutured the ends together with wire. König²⁶ used and recommended this method but for obvious reasons it is not applicable to elderly individuals, despite König's report of its successful use in a man of 70, since it entails an arthrotomy. Likewise the introduction of pegs, spikes, or screws which require opening of the joint is a formidable procedure. Fixation of the fragments with foreign material driven into the bone without opening the joint has likewise been practised sporadically for many years by many authors^{12,28,31,36} and while less formidable a procedure, was fraught with many difficulties.

In the use of nails, bolts or screws driven through the neck of the femur to fix the head, disadvantages were associated chiefly with the large amount of foreign material introduced into the bone. Erosion of metal or bone was not uncommon and inflammatory changes within the bone frequent. These difficulties resulted in a rather widespread objection to the use of any type of "hardware" for the fixation of fractures. In 1931, Smith-Petersen and his associates⁴⁵ presented a narrow 3-flanged nail for fixation of fractures of the neck of the femur. The nail was strong, and the flanges prevented rotation of the fragments, while the bulk of the pin was not great. The use of rustless steel in the manufacture of modern pins for fixation of fragments is a decided

advance, since steel of high chromium and nickel content apparently causes less reaction in tissues than other steel and is likewise less affected by the tissue fluids.¹⁵

Smith-Petersen and his associates opened the joint in order to introduce the pin and to effect approximation of the fragments.

Shortly afterward Sven Johannsen²⁰ made use of the Smith-Petersen nail for fixation of the fragments without opening the joint. Johannsen introduced a wire through the lateral aspect of the femur into the neck, as a guide for the introduction of the larger nail. The direction and position of the wire was determined by Roentgen ray, as was the length of the nail. This technique greatly simplified the procedure and permitted accurate placing of the nail without the necessity of opening the joint. Johannsen introduced the guide wire through the trochanter and into the head of the femur. A great many variations in technique have been devised. These have consisted chiefly in perfection of control of direction of the pin without the necessity of introduction of the guide wire.

Many authors prefer to insert the Smith-Petersen nail under fluoroscopic or radiographic control, without the use of the guide wire or other gadgets designed for direction of the nail.^{27,30,37,54} Others use protractors, templates or guides to direct the nail into position.^{4,8,11,22-24,41,51}

Some surgeons use multiple small stainless steel pins similar to Kirschner wires, the wires being inserted parallel to each other^{25,42} or at various angles.^{7,32,35a,b,49} The wires when anchored one to another tend to prevent retraction.

The question as to the need for impaction after reduction as suggested by Cotton¹⁰ is a controversial one. Most authors do not make a special attempt at impaction, but there are those who feel that this is an important adjunct.

The problem of anesthesia is likewise an important consideration. Inhalation anesthesia or spinal anesthesia is advocated by many, chiefly on the basis of the need for adequate relaxation to allow proper reduction. The time necessary for the actual reduction and pinning of the fragments is usually short enough that anesthetic difficulties are not of great magnitude. Others prefer local anesthesia, morphine and scopolamine, or avertin, on the premise that most of the patients are old and do not stand the anesthetic well. We have found, even in the case of a 99-year-old patient with a fracture of the neck of the femur, 50 mg. of novocaine intraspinally to be the anesthetic of choice and no untoward results were noted.

The problem of additional fixation following the apposition of the fragments by pins is widely discussed. Occasionally, the viewpoint is stressed that the patient should be permitted out of bed immediately and allowed to walk. This seems to be expecting a bit too much, although it is frequently advantageous to allow elderly patients out of bed in a wheel chair. However, even this is not usually essential since the patient, with relief of pain which is usual following fixation of the fragments, may be cared for in bed as well as old patients with any other condition. Following the insertion of the pin there is still the necessity for reparative processes before the neck of the femur is strong enough for full weight bearing. Frequently it is advisable, in addition to internal

fixation, to add some form of external fixation. We feel that where this seems advisable, temporary traction has one advantage in that it permits more freedom of motion on the part of the patient.

Difficulties which may arise following the insertion of a pin in the neck of the femur have been noted. Infection due to the pin retracting through the skin has been reported by Rowlette *et al.*⁴² and the pin has been found to have migrated into the bladder by Van Ravenswaay³⁹ and into the pelvis by Baeker-Gröndahl³ and Telson and Ransohoff.⁴⁹ However, these accidents are rare. More frequently, the pin tends to loosen and withdraw from the proximal fragment. To overcome this White⁵² devised a pin to hold the nail firmly in place and prevent retraction.

The use of various types of screws instead of pins has been revived chiefly on the basis that retraction is prevented. In addition, there are those who hold that the screw has an advantage over the nail because it is possible to draw the proximal fragment more firmly into approximation with the distal fragment.^{17,21,29}

During the past 7 years what has been incorrectly termed "blind nailing" has been accepted with enthusiasm. A rather voluminous literature is available. The enthusiasm for this lies in that the procedure is simple enough to permit its use in old debilitated individuals, fixation is assured, active and passive motion is possible, confinement to bed is lessened and due to the necessity for satisfactory reduction before fixation, pain is decreased. These factors have long been recognized as fundamentals in the treatment of fractures and especially in fractures of the neck of the femur.

The method has been widely accepted and many case reports are available. The results appear to be generally better than those obtained with other methods. This may be more apparent than real and one must wait until sufficient general experience has been gained and until adequately and carefully collected statistics are available. In general the outlook is good, since reduction must be obtained if the pin is to be introduced properly. In cases of treatment by fixation in abduction the emphasis all too frequently was placed upon applying the plaster with little regard for adequate reduction. For any method of treatment of fractures of the neck of the femur, fundamental principles demand reduction and fixation. Since adequate reduction is necessary for treatment by pinning or nailing the fragments together, it is quite likely that this most important deficiency, emphasized by Henderson,^{16a} with regard to treatment of fractures of the neck of the femur may be overcome.

It is much too early to attempt any evaluation of the end results of modern methods of internal fixation of intracapsular fractures as generally practised. That there will be not only a decreased mortality rate, but a higher incidence of bony union is suggested by the numerous enthusiastic reports now in the literature. However, it is not as yet apparent whether internal fixation will supply the solution to what Speed⁴⁶ has so aptly termed the "unsolved fracture." The optimism engendered by glowing reports may cause us to forget that we have long accepted as fact that the nutrition to the neck of the femur was poor

and healing difficult. The introduction of foreign material can only provide immobility of the fragments to permit repair to take place. It is quite possible that by the method of internal fixation with pins or nails the average surgeon may be able to approximate the results obtained by other methods in the best hands and that those more expert will improve their results.

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OPHTHALMOLOGY.

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INTRACRANIAL ANEURYSMS OF THE INTERNAL CAROTID AND OF THE CIRCLE OF WILLIS.

IN recent years, the study of aneurysms of the intracranial portion of the internal carotid and of the circle of Willis has assumed gradually increasing importance. Prior to 15 years ago, when Symonds'⁹ paper on the subject appeared, the diagnosis of intraeranian aneurysm was rarely thought of during the life of the patient. As recently as 1934, Garvey¹ reviewed the clinical symptoms, etiology, and pathologic findings in aneurysms of the circle of Willis and stated that, "the diagnosis of intracranial aneurysm cannot be made with any degree of certainty until rupture occurs." He considered, however, that the clinical syndrome produced by rupture of such an aneurysm was sufficiently characteristic to make diagnosis fairly certain. The use of arteriography offers an opportunity to confirm the diagnosis of an unruptured intracranial aneurysm during the life of the patient, and ligation of the internal carotid offers a possible means of preventing fatal rupture, if the diagnosis can be established. Involvement of vision, of visual fields, and of ocular muscles constitute the presenting symptoms in many of these cases. It is of interest, therefore, to review the ocular changes which suggest at least the possible presenec of an intraeranian aneurysm and to consider briefly the other diagnostic features which aid in confirming the diagnosis.

The charaeteristic syndrome of rupture of an intraeranian aneurysm is apparently that of a sudden apoplectic seizure with loss of conscieusness, vomiting, at times convulsions, followed by severe headache, photophobia, stiffness of the neek, and other signs of meningcal irritation. Examination of the spinal fluid reveals a uniformly bloody fluid under increased pressure. Complete paralysis of the oculomotor nerve with ptosis and iridoplegia is of frequent occurrence and is apparently indieative always of the side of the lesion. Frequently, large hemorrhages are found in the retina, espeecially around the optic disks. The hemorrhages may be of subhyaloid type and may be seen at times to break through into the vitreous. A mild edema of the optic disks may be present early and may increase in amount if the patient survives the attack. It is not clear why the characteristic hemorrhages in the retina are absent in some cases. But when they are present in

a patient who has had a sudden onset of coma followed by severe headache, the suspicion of hemorrhage into the subarachnoid space should always be aroused. The mechanism of these hemorrhages into the retina is not definitely known. Originally they were thought to be due to the extravasation of blood along the sheath of the optic nerve through the lamina cribrosa into the retina. However, Riddoch and Goulden⁷ have shown that the hemorrhages in the retina are due to obstruction of the central vein of the retina in the optic sheath with venous stasis in the retina and, at times, actual rupture of the walls of the retinal veins.

With the rather definite establishment of this syndrome of the ruptured aneurysm, more interest has centered recently on the possibility of diagnosis of the unruptured aneurysm. In 1925, Foster Moore⁶ reported what he believed to be the first case of unruptured intracranial aneurysm diagnosed during the life of the patient. This was a mycotic aneurysm which occurred during the course of a malignant endocarditis and which was found to involve the end of the right internal carotid artery and the beginnings of the anterior cerebral, posterior communicating, and ophthalmic arteries. The aneurysm had caused sudden, complete blindness in the right eye through rupture of the right optic nerve. Twelve days later there was an additional defect in the upper temporal field of the left eye.

A number of individual case reports have appeared in the literature from time to time, all of which are summarized in Jefferson's paper published in 1937. Most of these cases were diagnosed at operation or autopsy. As representative of various types of vision and field changes which may be encountered, the cases of Foster Kennedy,⁸ of Wetzell,¹⁰ and of McKendree and Doshay⁴ may be cited here. Kennedy reported a case simulating bilateral retrobulbar neuritis in which the loss of vision in the right eye preceded by 6 months that in the left eye. At exploration, the mass found was thought to be a glioma. Death occurred, however, following a rupture of the aneurysm which was found at necropsy in the right internal carotid artery. In Wetzell's case, there was secondary optic atrophy in the left eye with vision reduced to 6/60 and with progressive concentric contraction of the visual field. At necropsy, which in this case also followed rupture of the aneurysm, the left optic nerve was found markedly stretched and flattened over the surface of a large aneurysm of the left internal carotid artery.

In the 3 cases reported by McKendree and Doshay, the ocular findings were those of progressive chiasmal lesions with bitemporal hemianopic field defects. All of these cases were discovered at operation following the diagnosis of chiasmal lesions of indeterminate type. In 1 of the cases, the presence of the aneurysm was confirmed at necropsy following rupture. In another case, exploratory craniotomy revealed an aneurysm of the left internal carotid artery. Following a period of digital compression, the left common and internal carotid arteries were ligated. The left eye had been blind before the operation and remained so, but the temporal field of the right eye had widened out considerably 3 months after the ligation. In 1 of the cases, Roentgenograms of the

skull were negative; in 1, erosion of the sella and clinoid processes was present; in the third, there was decalcification of the dorsum sellæ. In all of the cases, encephalographic studies demonstrated the site of the lesion but not its nature.

With the aid to diagnosis furnished by careful and expert roentgenographic studies, encephalographic studies, and arteriograms, it is becoming possible to diagnose at least a certain percentage of cases of unruptured intracranial aneurysm during life. In 1926, Sosman and Vogt⁸ called attention to the roentgenographic diagnosis of aneurysms of the internal carotid artery and the circle of Willis. They said, "The recognition of these aneurysms on Roentgen examination is by means of (1) calcification in the wall of the aneurysm, or (2) erosion of the bone adjacent to the aneurysmal sac. In the first, one can see thin plaques of calcium, usually semilunar in shape, with their convexity upward, lying beside the sella, or should the aneurysm be large, rising above the level of the sella, but just to one side of it. These are fine curvilinear shadows, sharply outlined, occasionally segmented, and easily recognizable as being in the wall of a cystic or rounded structure. . . . The erosion due to these pulsating sacs . . . involves or may involve one anterior clinoid, the lateral half of the body of the sphenoid on the same side, and a similar portion of the posterior clinoid. . . . There is no expansion of the pituitary fossa . . . and no apparent depression of the floor of the fossa. The opposite anterior clinoid is not involved . . . and there is no pressure atrophy or forward bending of the posterior clinoid."

Sosman and Vogt admitted that roentgenographic diagnosis was not uniformly successful in the cases they reported. They estimated that in 25 % of the cases, diagnosis was possible from the roentgenographic findings and that, in an additional 25 %, the roentgenographic findings would support the clinical impression. They expressed the belief that with improvement of technique, roentgenographic diagnosis would be possible in a higher percentage of cases. This belief would seem to be supported by the results in a more recent series of cases, that of McKinney, Acree and Soltz.⁵

In 1936, McKinney, Acree and Soltz reported 8 cases of unruptured aneurysm of the intracranial portion of the internal carotid artery proximal to the point where it leaves the roof of the cavernous sinus. All of them had paralysis of the third and fourth nerves, 6 had paralysis of the sixth nerve, 5 had exophthalmos on the side of the lesion, 4 had pallor of the disk, 2 had low-grade papilledema, 1 was blind, and 5 had contracted fields on the side of the lesion. All had corneal anesthesia and pain and paresthesias over the eye. They consider that the clinical syndrome of an unruptured aneurysm of the intracranial portion of the internal carotid artery consists of exophthalmos and a partial or complete involvement of the second, third, fifth and sixth nerves on the side of the aneurysm. The third and fifth nerves are involved, always, the others usually. Since the internal carotid artery gives off branches in the cavernous sinus to the third, fourth, sixth and first divisions of the fifth nerve, the paralysis may be on a vascular as well as a pressure basis. Aneurysms in this location may extend into the

ophthalmic artery but such extension is not necessary to produce the syndrome described. All of their cases had confirmatory roentgenographic findings. In addition to the curvilinear plaques of calcification and the unilateral erosion of the sella described by Sosman and Vogt, they called attention to the presence of enlargement of the sella, unilateral enlargement of the optic foramen and of the superior orbital fissure, erosion of the margins of the carotid canal, and displacement of the pineal.

Jefferson² agrees substantially with McKinney, Acree and Soltz on the roentgenographic diagnostic signs of intraeranian carotid aneurysms. He calls attention also to the value of angiography in definitely localizing the aneurysm. He has divided his 53 intraeranian aneurysms into four groups: (1) Pure subarachnoid hemorrhage with nothing to indicate the precise site of the aneurysm, 16 cases; (2) aneurysms with paralysis of cranial nerves, usually the third, 9 cases; (3) sacular (non-fistulous) aneurysms of the internal carotid in the cavernous sinus, 16 cases; and (4) basal aneurysms with affection of the visual pathways, 12 cases. His paper is devoted essentially to the detailed consideration of the 12 cases in the last group, in which, as in the third group, the symptoms of the aneurysm are essentially those of a tumor.

Jefferson thinks that the most important division of carotid aneurysms is into supraclinoid and infraclinoid. The infraclinoid aneurysms arise in the cavernous sinus and give rise to ophthalmoplegia and disturbances of the trigeminal nerve. Visual difficulty is caused essentially by paralysis of accommodation or by diplopia. Supraclinoid aneurysms spring from the carotid at the origin of the ophthalmic or posterior communicating arteries or at the final bifurcation of the main trunk. These are the aneurysms which interfere primarily with vision. Jefferson further subdivides them into four groups: (1) Those interfering with the optic radiation and striate cortex, 3 cases; (2) those compressing the optic tract, 1 case; (3) those affecting the optic nerves, 2 cases; and (4) those involving the chiasma, 6 cases.

In the first group, Jefferson includes cases of homonymous hemianopsia following subarachnoid hemorrhage. He believes that the hemianopsia is the result of thrombosis of the posterior or middle cerebral artery following the rupture of an aneurysm. Jefferson considers as indicative of pressure on the optic tract a left homonymous hemianopsia which was found in association with a right third nerve paralysis and a left hemiparesis in an aneurysm of the right posterior cerebral artery immediately outside the third nerve confirmed at necropsy following death from rupture of the aneurysm. Of the 2 cases with unilateral loss of vision, the onset was gradual in 1 and sudden in the other. The case with gradual loss of vision was proved at necropsy to be due to a large aneurysm of the internal carotid artery in the anterior end of the cavernous sinus. Both these cases also had paralysis of the third nerve on the side of the lesion. Wetzel calls attention to the fact that this unilateral loss of vision is due to the fact that the optic nerve rests inferiorly on the internal carotid artery at the point at which the latter forms an arch with the convexity upward and gives origin to the ophthalmic artery.

Of Jefferson's 6 cases with signs of compression of the chiasm, 3 showed bitemporal hemianopsia, 1 was blind in one eye with temporal hemianopsia in the other eye, 1 had bilateral inferior altitudinal anopsia with relative bitemporal hemianopsia, and 1 had unilateral central scotoma with relative bitemporal hemianopsia. Four of these cases were confirmed by operation and 2 by angiograms with thorotrast. It is of interest that in 2 of these cases the eye on the side opposite to the aneurysm showed the earliest and greatest loss of vision.

Jefferson thinks that pain and headache are more frequent and symptoms severe in patients with aneurysms than in those with pituitary tumors. The characteristic anesthesia of the ophthalmic division of the fifth nerve which is so frequent in subclinoid aneurysms does not occur in supraclinoid aneurysms. Hemiparesis is rare. Mental changes are frequent. Paralysis of the ocular muscles occur in supraclinoid aneurysms but are not as frequent as in the subclinoid type. Anosmia is very infrequent. Hypothalamic signs and evidences of dyspituitarism are rather rare.

Ligation of the carotid is gradually being recognized as the only valuable method of treatment for cases of intracranial carotid aneurysms. Jefferson believes that this is true in spite of the fact that he ligated only 1 of the cases in the present series (with definite improvement in vision). Because of the risks involved in ligation of the carotid, he thinks that only those cases should be ligated in which there is progressive failure of vision or persistent pain. Before ligation, it should be demonstrated that digital compression for 30 minutes is tolerated without ill-effect. It is well, Jefferson thinks, to do the ligation under local anesthesia so that the effects of a temporary ligature can be observed for a full hour before the final ligature is applied. It should be remembered, however, that even this procedure does not always prevent the development of a hemiplegia or aphasia 36 to 48 hours after the ligation.

Summary. It seems rather obvious that there are two relatively distinct locations of intracranial aneurysms in which the types of ocular involvement are at least relatively if not entirely distinct. Saccular aneurysms of the internal carotid in the cavernous sinus or just at the point of exit produce essentially oculomotor paralysis. Aneurysms of the internal carotid at the point of origin of the various branches of the circle of Willis or of the ophthalmic artery produce ocular syndromes of chiasmal or prechiasmal type with characteristic field defects. Aneurysms which cause primarily oculomotor rather than visual field defects seem to be the ones most frequently associated with recurrent hemorrhages into the subarachnoid space and retina. Aneurysms in this location probably respond more favorably in the main to ligation of the carotid than do aneurysms located higher in the circle of Willis. Paralysis of the third nerve is a more reliable localizing sign of the side of the aneurysm than is the character of the defects in the visual fields, unless the loss of vision is entirely unilateral.

HENRY P. WAGENER, M.D.

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THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

SEPTEMBER, 1938

ORIGINAL ARTICLES.

LATE RESULTS IN TREATMENT OF AMEBIC ABSCESS AND
HEPATITIS OF THE LIVER.

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SUCCESS in the treatment of amebic abscess of the liver may be held to be some measure of the efficiency of the procedure employed. Certainly invasion of the liver by the parasite—an indication of its extension beyond the wall of the bowel—is a serious manifestation of the disease. Evidence of this is afforded by the high mortality which occurred prior to the introduction of emetine by Sir Leonard Rogers.⁴ Although emetine serves to control the acute manifestations of the infection, it has been difficult to eradicate the parasite completely. We have reported, from time to time, improvements in treatment which have proved most effective, but we were curious as to the late results we had obtained among patients who had hepatic involvement. In reviewing the records of the past 18 years we find that 18 patients who had an abscess of the liver have come to operation and that 17 others have been regarded clinically as presenting signs of hepatic involvement. Drainage or aspiration of an abscess of the liver with identification of the ameba in the pus is definite proof but it is not possible to prove actually that hepatic damage occurred in the patients not operated on.

One might expect that amebic abscess of the liver would be uncommon in the North Temperate Zone. Hence, it was surprising to

find that the ameba was the cause of the abscess in 18 (14%) of 125 cases of abscess of the liver encountered at The Mayo Clinic. The actual incidence of amebic abscess of the liver and hepatitis in relation to amebiasis itself is small, that is, approximately 2 or 3% of the cases, in our practice. This would seem a fairly accurate incidence for the north, barring massive infections such as occurred in the Chicago epidemic, but is, by no means, indicative of what may be the incidence in the south and in the tropics.

That the resistance of women is greater than that of men would again seem to be substantiated among patients who have hepatic damage due to the ameba. Of the 18 surgical patients, all were men and only 4 of the 17 medical cases were women; thus, 4 of the 35 patients were women. Although age is of no particular importance, the average is in the fourth decade with a range from 17 to 59 years. It has been noted in similar discussions that an associated or even antecedent diarrhea may be absent. It bears repetition to stress that 8 of these 35 patients did not have diarrhea; nor was there a history of diarrhea. Pain, usually in the right upper quadrant, was the most frequent symptom. Pain also was noted in the lower right portion of the thorax, epigastrium, and in the left upper quadrant. Reference of pain to the right shoulder was noted in 8 instances and to the left shoulder in 1 instance, indicating diaphragmatic irritation. Likewise, fever was a common symptom, although not present in 4 cases at the time of the patient's admission. Fever associated with chills had occurred in 15 cases.

The composite picture is that of a middle-aged man, with or without a history or the presence of diarrhea, who suffers with pain in the upper right quadrant. This pain is a steady soreness which varies in intensity but is not like the colic usually associated with disease of the gall bladder. Fever, 1 to 5° above normal, is associated with the pain. The pain is likely to be referred to the shoulder. Leukocytosis is present but both fever and leukocytosis may be minimal during a quiet phase. On physical examination there may be tenderness of the liver which may be elicited only by compressing the lower ribs or by a thrust of the examining hand against the liver when the patient inspires deeply. Roentgenologic examination of the chest may reveal elevation of the right half of the diaphragm and may even give evidence of fluid in the lower right portion of the thorax (10 of 29 cases). A mass in the region of the liver or enlargement of the liver is often present (8 of 35 cases). Occasionally, a draining sinus, the walls of which seem to be disintegrating, is present, if an operation has been performed previously (9 of the 18 surgical cases). Jaundice may be present but it is not intense (noted in 9 of 33 cases). Examination of the stool and pus from the abscess, if available, should be positive although repeated search may be required. In this series, criticism may be directed toward the fact that stools positive for the ameba were found in only 26

cases. In 6 additional instances, pus from the abscess was found to contain the parasite. The 3 patients, examination of whom gave no actual proof that amebas were present in stools or pus, responded so characteristically to antiamebic treatment that we make no apology for including them. "Never" is a poor word to use but, to date, we have "never" seen any disease that is so definitely improved by treatment within 36 to 48 hours as amebiasis after emetine is administered (3 to 4 grains); this improvement is apparent to both patient and physician.

As additional evidence of severity of infection, if the patient's condition permits, ulcers may be visualized through the proctoscope (7 of 17 patients examined) and the barium enema may show ulcerative changes, usually in the cecum (3 of 13 patients examined). In our series, the patients who were severely ill were not examined by these two methods.

If it is known that the liver is damaged, the extent of such damage may be determined partly by use of the bromsulphalein test. Of 7 medical cases, 5 did not give evidence of retention of the dye and 2 gave evidence of retention graded 1 to 2 (on the basis of 1 to 4). Of 6 surgical cases, 3 gave evidence of retention of dye graded 1, 2 graded 2, and 1 graded 4.

Result of Treatment in Medical Cases. Fourteen of the 17 patients are available for study of late results. Of the remaining 3, 1 died within 32 hours after admission. He was *in extremis* and so little could be accomplished that the diagnosis of perforation of amebic cecal ulcers and amebic abscess of the liver was not established until necropsy. The other 2 patients were seen in 1919 and in 1922 and we could obtain no recent data. The results of treatment of the remaining 14 patients may be noted in Table 1.

TABLE 1.—RESULTS: MEDICAL TREATMENT OF AMEBIC INFECTION OF LIVER.

Case No.	Date first seen.	Latest information.	Condition.
1	1933	Dec., 1937	Apparently well
2	1934	1935	Apparently well
3	1934	Jan., 1938	Apparently well
4	1932	Jan., 1938	Apparently well
5	1935	Jan., 1938	Apparently well
6	1934	Jan., 1938	Apparently well
7	1934	Months later	Unknown
8	1932	Dec., 1937	Apparently well
9	1933	Dec., 1937	Apparently well
10	1934	Sept., 1937	Apparently well
11	1934	Jan., 1938	Apparently well
12	1935	Jan., 1938	Apparently well
13	1935	Dec., 1937	Apparently well
14	1928	Months later	Unknown

It would be presumptive for us to use the word "cure"; but it is encouraging to have this group, each member of which gave clinical evidence of a serious condition which disappeared, as if by magic,

after antiamebic treatment. In view of their history of symptoms antedating treatment and the fact that little, if any, difficulty has been experienced since then, one cannot help but feel that a suitable régime has been employed. One example should be mentioned which might be considered as a damper against unwarranted therapeutic claims. Case 6 represents the only patient in this medical group concerning whom the question of adequate antiamebic therapy was raised and in whom the classical signs of hepatic damage later developed. He was seen at the clinic, for the first time, in 1926 because of bloody diarrhea which was found to be due to *E. histolytica*. He received emetine and 4 times he received a course of 15 tablets of stovarsol. The response was characteristically excellent and he remained well until December, 1933, at which time he developed pain in the region of the liver. On readmission, in March, 1934, examination of the stools again gave positive results for *E. histolytica*. There was marked tenderness over the left lobe of the liver and he had fever and leukocytosis. Emetine and treparsol were administered and all symptoms abated; in 48 hours he said he felt well. Further treatment with emetine and treparsol was carried out at home and on his visit here in January, 1938, he was in fine health. Examination of stools gave negative results for *E. histolytica*. We are inclined to consider this patient as an example of reinfection rather than one of exacerbation, because he has been well for 7 years.

We do have record of 3 of this medical group who had received some antiamebic therapy but it had been scanty and unsystematic; such treatment, we know, is not conducive to good therapeutic results. Although 2 or 3 years may be too short an interval of time to permit unwarranted therapeutic claims, yet the illness that preceded treatment in each case and the good health subsequent to treatment make it difficult to avoid enthusiasm.

Surgical Cases. Considering the surgical aspect of these 18 patients, one is impressed by the difficulty encountered in establishing a correct diagnosis. We realize that amebic abscess of the liver is, by no means, as frequently a surgical problem as disease of the gall bladder, ruptured ulcer, or even a lesion in the hepatic flexure of the colon, yet the presence of an abscess in that region should arouse suspicion. Usually the pus is characteristic, a dark reddish, chocolate-colored material which is rather thick. This material continued to drain from several patients without decreasing in amount, as one would expect of a pyogenic abscess. With persistence of drainage, there may be a melting away, a digestion, of walls of the sinus tract. In 1 instance, this had progressed until the patient had a hole in his epigastrium large enough to admit a fist. The digestive feature was recognized and attributed to pancreatic ferments from drainage of what was probably a pancreatic cyst. When the thick, dark, sullen flowing pus finally was examined for amebas, the

problem was settled and after treatment was instituted, filling in of the huge hole was merely a matter of a few days.

The presence of fluid in the right side of the thorax has proved misleading. Drainage through the region of resected ribs has been undertaken, the opening later being enlarged, and the etiologic factor being discovered only after the pus was examined for amebas. Also, we have had the experience of pus obtained from a draining sinus being sent "for culture" and for the usual bacteriologic studies, which delayed diagnosis for days until it was reported that "amebas have not been found." Apropos of this, Magath³ has pointed out to us that the first pus obtained, or even that from a dressing is not likely to reveal the parasite; he makes a practice of obtaining material from the sides or edges of the sinus tract, because it is there that the parasite is working and living. We are apt to forget that the word "histolytica" means "dissolving tissue" and, therefore, it is not surprising that *E. histolytica* stays close to its base of supplies, in the walls of the sinus tract.

Eleven of the 18 patients had been operated on prior to admission to the clinic. One of them was a patient whose condition we had diagnosed as amebic colitis and who returned home to carry out treatment. He failed to complete his regimen and developed a mass in the region of the liver which his doctor drained through the side. Two patients had received much antiamebic treatment but before admission to the clinic, in spite of the treatment, an abscess had developed which was aspirated in one case and drained in the other. In both, the abscess persisted and was present on admission to the clinic. Eight of the patients stated that abscesses of unrecognized etiology had been drained and the drainage had persisted from 1 to 10 months. It was remarkable that 7 of these 8 patients had maintained even a moderately fair level of resistance. The resistance of the eighth patient was greatly depleted even though his abscess had drained for only a month. Effort was made to afford better drainage and he also received 6 grains of emetine hydrochloride, but to no avail, and he died within 48 hours.

Three patients who had been operated on elsewhere and who, when admitted, had draining sinuses, were not operated on here. Examination of material from the walls of the sinus revealed the parasite and institution of antiamebic therapy relieved the surgeon of further care of the patient. Operations were undertaken at the clinic on 15 patients. We noted, in the preceding paragraph, the patient *in extremis* who died within 48 hours. A second patient underwent drainage of a large right subphrenic abscess and only after some further time elapsed was the pus examined for amebas. Specific treatment was administered over a period of about 3 weeks but was of no avail in preventing his death.

The following operations were carried out on the remaining 13 patients: aspiration of the left side of the thorax (2 cases), estab-

lishment of drainage through resection of a low right rib (4 cases) on the lateral side, and drainage through the abdomen (7 cases). Antiamoebic treatment was instituted as soon as the diagnosis was established.

The most dramatic case that we have encountered was that of a man (reported previously) who, when first seen at the clinic, was unable to lie down; he was thin and very weak. He was scarcely able to breathe because of a constant cough productive of thick, dark-colored, foul-smelling sputum. On the lower right portion of the thorax were scars of a recent rib resection. He had a moderate diarrhea which added to his sorrows. The temperature was 100.5°F . (38.1°C .) and the pulse rate was 150 beats per minute. The preliminary suggestion had been made that carcinoma of the lower lobe of the right lung was present. An alert resident physician had sent the sputum and stool for examination for amebas. *E. histolytica* was present in the stool and immediately treatment was begun. Twice, the lower right portion of the thorax was aspirated and, following these procedures, the abscess ruptured spontaneously through the old scar. Release of much purulent material, in which *E. histolytica* was identified, contributed greatly to the patient's relief. He remained here for several weeks at the end of which time he seemed to have recovered completely. A report, 2 years later, spoke of no further trouble. In this patient, the abscess of the liver had ruptured through the diaphragm and into the bronchial tree.

The question often arises, if you could establish the diagnosis, could not operation be avoided? Yes, we feel it might, as judged on the basis of experience with the 18 medical cases. On the other hand, occasionally there was a patient (2 in our series) of whom abscess of the liver was suspected. Much antiamoebic therapy was administered; yet, neither of these 2 patients was able to absorb the large collection of fluid and, therefore, open drainage was necessary. In fact, 1 patient had undergone aspiration of the region of the abscess three times, only to suffer prompt refilling of the cavity. The general impression must hold that development of an abscess is unlikely if the patient has received adequate treatment. The 2 patients first mentioned must be exceptions that prove the rule.

Table 2 summarizes data concerning the 18 patients who underwent operation. The treatment of 1 patient (Case 16) must be considered a failure. Following operation and treatment at the clinic in 1919, he remained in apparently excellent health until 1925 when he had an attack of bloody diarrhea which was diagnosed as amebiasis. This was fairly well controlled until 1931 when another abscess of the liver developed. We are indebted to his physician for the data of 1925 and 1931. Again the question arises concerning whether this represented a relapse (6-year interval) or a reinfection.

As a corollary, we have record of 4 patients (all men), who gave a history of having undergone an operation for amebic abscess of the

liver. One patient (seen at the clinic in 1925) was operated on in South Africa in 1906 and must represent one of the few persons who were hardy enough to survive what was probably amebic infection in days when no specific treatment was known. A second patient had undergone drainage of an abscess on three occasions in a period of 3 years. At this time, he was having moderate diarrhea and beginning to sense pain in the region of the liver. *E. histolytica* was identified in the stool. Treatment was apparently successful and, 10 years later, he reported no further trouble. A third patient had undergone drainage of an abscess of the liver in 1927, followed by some antiamebic treatment. On examination in 1929, there was no evidence of abscess of the liver but he did have a granulomatous mass in the rectum which, it was thought, might be carcinoma.

TABLE 2.—RESULTS: SURGICAL TREATMENT OF AMEBIC ABSCESS OF LIVER.

Case No.	Date first seen.	Date last report.	Condition.
1	1928	1930	Apparently well
2	Oct., 1936	Dec., 1937	Apparently well
3	Aug., 1937	Jan., 1938	Apparently well
4	1920	1937	Apparently well
5	1925	1937	Apparently well
6	1924	1928	Apparently well
7	1930	1938	Apparently well
8	1929	1938	Apparently well
9	1931	1938	Apparently well
10	1930	1938	Apparently well
11	1927	1938	Apparently well
12	1927	1935	Apparently well
13	1928	1937	Apparently well
14	1930	1937	Apparently well
15	1928	1934	Well (died of other causes)
16	1919	1932	Recurrence? 1925
17	1925	Died post-operatively	
18	1932	Died post-operatively	

E. histolytica was identified in the stool and specific treatment brought about an apparent cure. The fourth patient gave a history of having had an abscess which had been drained on two occasions and he stated that it was amebic. He had no evident amebiasis when examined at the clinic. Hence, some few patients may not only survive operation for unrecognized amebic abscess of the liver but have little or no further trouble. These must be hardy, tough individuals and one cannot bank very heavily on such good fortune to often repeat itself. Even though it may be all but impossible to make a correct preoperative diagnosis, microscopic examination of the pus from any liver or right pleural abscess should quickly establish the diagnosis. It bears repetition to urge care in obtaining material for examination and not to be turned aside too easily by one report of negative findings. It is not scientific medicine but a

life may be saved by empirically administering emetine, if skill in the recognition of *E. histolytica* is lacking.

Another question has been raised regarding the danger of using arsenic in the presence of amebic abscess of the liver. Our experience obviously is small, as represented by these few cases; in fact, 3 of the 18 surgical cases were encountered before we used arsenic routinely. We can state, however, that we have seen no untoward results from the use of arsenic. On the contrary, we have seen failure to respond rapidly and fully until arsenic was administered. There is always the factor of individual tolerance to the drug, for which one must always be on guard, but, other than this, we have no hesitancy in advising the use of arsenic. One might coin the slogan, "Emetine to check the acute symptoms and arsenic to wipe out the amebas." Our present method of treatment is summarized as follows:² "If the patient is quite ill, he is kept in bed for the first few days; if he is not particularly ill, hospitalization is not necessary. Obviously the diet may need to be bland and simple if there is much dysentery, but very rapidly, that is, within 24 to 48 hours, a full and generous diet is begun. . . .

"If the patient has not received antiamebic treatment recently, he is given 0.065 Gm. (1 grain) of Burroughs, Wellcome & Co. emetine hydrochloride, subcutaneously, twice daily for 3 days. After an interval of a week, 0.043 Gm. (two-thirds grain) of emetine is given twice daily for three more days. With the institution of the emetine, treparsol, 0.25 Gm. (4 grains), is administered orally with each meal for four days. If there is no intolerance to arsenic, two more such courses are prescribed with intervals of ten days between the courses. . . .

"If stool tests are positive following this regimen, three courses of chiniofon are prescribed: 3 Gm. orally per day for a week and repeated for two more such courses, with a week's interval between courses. If diarrhea is increased, the daily dose is decreased, thereby prolonging each course. Failure after this would indicate a course of one injection of arsphenamine weekly for six weeks, and 1 drachm (3.88 Gm.) of bismuth subnitrate from three to six times daily during the period."

Summary. Invasion of the liver by *E. histolytica* is a serious complication of amebic infection. The diagnosis of involvement of the liver is suggested by the symptoms of pain in the upper part of the abdomen, often referred to the shoulder, by fever, chills, leukocytosis, and, usually, but not always, an associated diarrhea or history of diarrhea. Unless an abscess develops which is aspirated or drained, it is not possible to prove that the liver is involved. However, such a syndrome as listed above, which is relieved by antiamebic treatment is all but proof of amebic infection. As a corollary, a similar picture uninfluenced by antiamebic treatment is not amebiasis, except in the rare instances of a huge collection of

pus which must be drained and then, of course, the proof of *E. histolytica* should be promptly obtained. Faith in the efficacy of our medical treatment would seem supported by the results in these cases; not that we have ceased trying new drugs, but until just as effective ones with even less toxicity than we now encounter are available, we feel justified in considering emetine and treparsol as the backbone of our treatment.

Regarding our surgical cases, it is obvious both from clinical experience as well as from this review, that the correct preoperative diagnosis of amebic abscess of the liver is by no means easy. However, if the surgeon encounters an abscess in the upper right portion of the abdomen, the source of which is not obvious or, if there is fluid in the thorax (as a result of extension from the liver through the diaphragm) and the material from the abscess is thick and dark in color, it is difficult to think of allowing such an abscess to remain undiagnosed without performing an examination for *E. histolytica*. Figures will vary with material available for study but probably 10 to 15% of abscesses of the liver seen in the North Temperate Zone are due to *E. histolytica*.

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THE "HEMATOPOIETIC PRINCIPLE" IN THE DISEASED HUMAN LIVER.*†

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IN 1932, Richter, Ivy and Kim³ reported the présence of the "specific anti-anemic substance" in an extract obtained postmortem from the liver of a treated case of pernicious anemia and its absence from the liver of an untreated patient with this disease. They assumed, therefore, that when the specific anti-anemic substance is administered to a patient with pernicious anemia the liver stores it. Their observations were confirmed by Wilkinson and Klein⁴ and by Goldhamer, Isaacs and Sturgis.¹

* Presented by title before the meeting of the American Society for Clinical Investigation, Atlantic City, May, 1937.

† This study was made possible by a special grant from Parke, Davis & Co.

Wintrobe and Shumacker⁶ (1933), and Wintrobe⁵ (1936) called attention to the association of macrocytic anemia and liver disease and on the basis of clinical and pathologic studies advanced the hypothesis that this anemia may be due to inability of the diseased liver to store the anti-anemic substance. As far as we were aware, the only direct proof of this assumption was the observation of Goldhamer, Isaacs and Sturgis that an extract prepared postmortem from the liver of a patient with cirrhosis and macrocytic anemia was ineffective in eliciting a hematopoietic response when administered parenterally to a patient with pernicious anemia in relapse. This observation, together with other experimental data, led them to conclude that the specific hematopoietic substance might not be stored by a severely damaged liver, or even though stored, might not be delivered to the tissues. It therefore appeared to us desirable to obtain additional data on the presence (or absence) of the anti-anemic substance in the diseased human liver.

Method. Extracts were made from a normal calf's liver and from 5 diseased human livers according to the following method, kindly furnished us by Dr. Raphael Isaacs,² which is essentially that of preparing Cohn's fraction G: "Suspend 500 grams of liver finely chopped in 1 liter of water and stir thoroughly. Heat this on a steam bath to 80° C. until the protein appears to be precipitated. Filter. Add enough concentrated hydrochloric acid to the filtrate to precipitate the acid-coagulable protein. Filter. Concentrate under reduced pressure to 300 cc. and add enough 95% alcohol to make the solution 70% alcohol. Filter. Remove the alcohol under reduced pressure. Concentrate the remaining fluid to 100 cc. Filter."

The patients selected for injection had typical pernicious anemia with a red cell count between 1 and 3 million per c.mm., had received no anti-anemic treatment in the form of liver, iron, arsenic or transfusions for at least 1 month prior to the injection, were free of infection (with one exception) and subsequently showed a complete remission under specific treatment.

Before preparing the extracts of the human livers, a control extract was made from a normal calf's liver and administered intramuscularly to a patient with pernicious anemia. A satisfactory response was obtained (Fig. 1).

Extracts were then prepared from the livers of the following patients with hepatic disease:

CASE 1. *Extract from G. H. (No. 360238), patient with hepatic cirrhosis.* The patient was a male, aged 54 in whom a diagnosis of hepatic cirrhosis was made 2 years prior to death. The diagnosis was based on the presence of an enlarged firm liver and an enlarged spleen together with a strong alcoholic history. The blood Wassermann test was negative. There was no anemia and no history of hematemesis. On March 1, 1936, he was hospitalized because of ascites. At that time, the red count was 3 million, the hemoglobin 68% (Sahli) and the M.C.V. 105. A post-histamine achlorhydria was present. There were no abnormal neurologic findings. There was 20% retention of bromsulphalein $\frac{1}{2}$ hour after injection of 2 mg. of the dye per kg. of body weight. The Takata-Ara test was positive. The

icteric index was 11. On March 31, and again on April 1, 1936, he was given 2 cc. of a commercial liver extract intramuscularly (of which 1 cc. was derived from 100 gm. of liver) but no hematopoietic response was obtained. He was given 3 additional injections of 1 cc. of this liver extract during April, 3 in May, 2 in June and 4 in July (the last on July 31st), in spite of which there was a progressive increase in the anemia. A Talma-Morrison operation was performed on May 19th, at which time a "marked atrophic cirrhosis" was described. On August 30th, the day before death, the red cell count was 2.2 million, hemoglobin 47% and the M.C.V. 100. The patient died in coma on August 31, 1936.

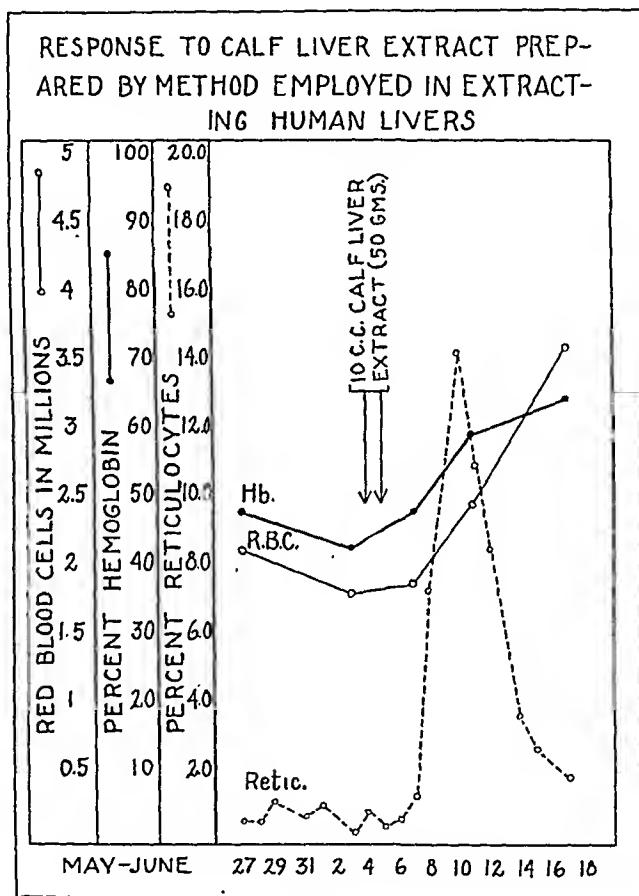


FIG. 1.

Necropsy (4 hours after death): The liver was described as small, pale yellow and finely nodular, and weighed 900 gm. Microscopic examination revealed extensive fibrosis with lymphocytic infiltration.

An extract prepared from the liver and administered intramuscularly to a patient with pernicious anemia produced a typical response (Fig. 2).

It may be argued that the hematologic response could be ascribed to the administration of the commercial liver extract, even though none had been given for a month prior to the patient's death. Regardless of this, the response obtained would indicate the ability of a diseased liver to store the anti-anemic substance.

CASE 2. *Extract from L. K. (No. 16423), patient with hepatic cirrhosis.* The patient was a painter, aged 32, who was first admitted to the medical service on December 24, 1933, because of hematemesis. He had had intermittent digestive distress including pain in the epigastrium occurring immediately after meals for 4 years. There was a strong history of alcoholism. He was found to have an enlarged liver and spleen with no evidence of ascites. There was 30% retention of bromsulphalein $\frac{1}{2}$ hour after the injection of 2 mg. of the dye per kg. of body weight. The icteric index was 11. The blood Wassermann test was negative. A gastro-intestinal Roentgen ray series showed no evidence of peptic ulcer. The blood count on discharge was 3.2 millions with 45% hemoglobin. The gastric contents contained free hydrochloric acid.

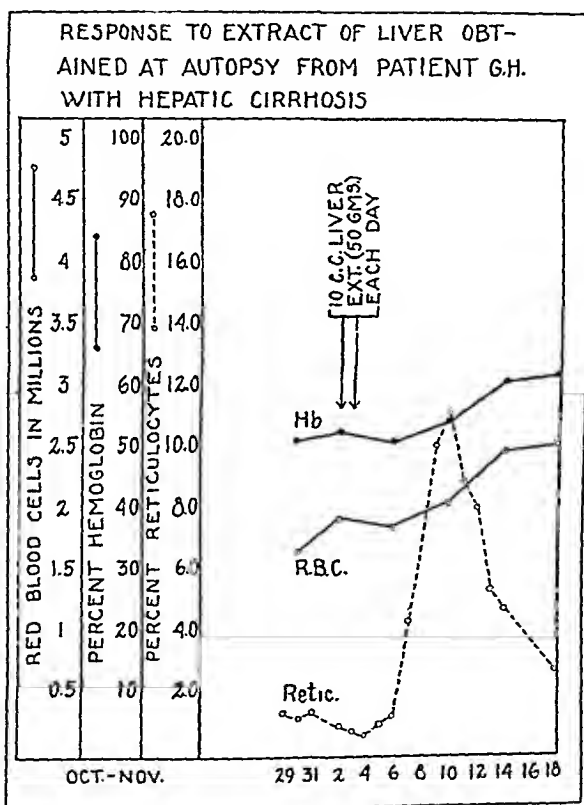


FIG. 2.

He was again seen on June 11, 1935, at which time he presented much the same findings except that his liver was not palpable, there were very prominent superficial veins, and ascites and slight icterus were present. The icteric index was 19. The Takata-Ara test was positive. The blood count showed 60% hemoglobin with 2.9 million red cells. Macrocytosis was prominent in the stained blood smear. The M.C.V. was 100. The patient died 6 days after admission following massive hematemesis. He had at no time during his illness received any anti-anemic therapy other than iron.

At *necropsy* a ruptured esophageal varix was demonstrated. The liver, which weighed 1600 gm., was described as tawny yellow, coarsely nodular and of extremely firm consistence. Microscopic sections revealed extensive fibrosis, lymphocytic infiltration and apparent bile duct proliferation.

An extract prepared from this liver yielded a satisfactory response when administered intramuscularly to a patient with pernicious anemia (Fig. 3).

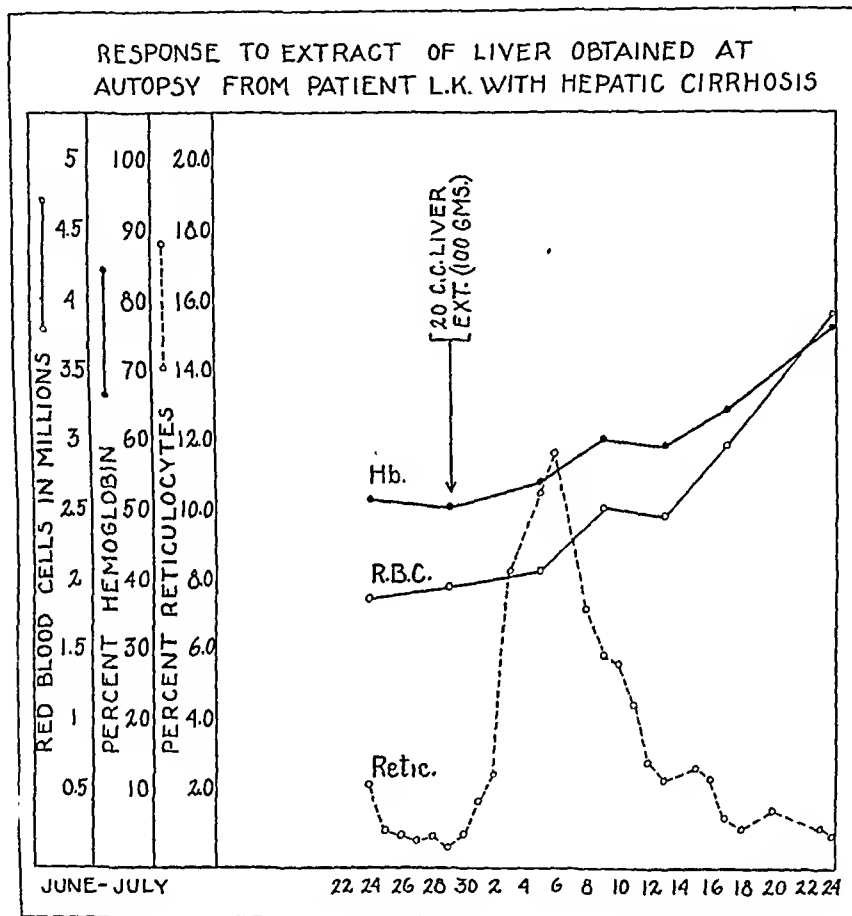


FIG. 3.

CASE 3. *Extract from F. R. (No. 28478), carcinoma of the hepatic duct with cirrhosis and hepatic metastases.* The patient, F. R., a female nurse aged 45, was admitted to the medical service of this hospital on September 7, 1934, complaining of jaundice of 1 week's duration which had been preceded for several days with fever, chills, nausea, diarrhea and abdominal pain. There was no history of alcoholism. There was a history of nervous indigestion following a back injury 3 years before. Her liver was found to extend about 2 cm. below the right costal margin, while the spleen was not felt. The icteric index was 100 and the serum bilirubin 16.5 mg. %. The blood Wassermann test was negative. The hemoglobin was 90% and the red count 4.4 millions. It was at first felt that the patient had catarrhal jaundice, but because of progressive increase in the icterus (icteric index 165, serum bilirubin 25 mg. %) laparotomy was performed 1 month later. An inoperable tumor occluding the hepatic duct was found. Following operation, the jaundice remained completely obstructive as verified

by repeated stool and urine examinations. In April, 1935, the spleen became palpable and in May, ascites developed. The bromsulphalein retention varied between 80 and 100% throughout her stay. Anemia gradually developed, the red count varying between 2.8 and 3.5 millions, the hemoglobin between 61 and 70%, and the M.C.V. between 102 and 111. Free hydrochloric acid was present in the gastric contents.

The patient died in coma on July 4, 1935. The liver was described as "smaller than average," yellowish red and of increased consistence. Microscopic sections revealed diffuse fibrosis and scattered metastases.

An extract administered intramuscularly to a patient with pernicious anemia produced the effect as noted in Fig. 4.

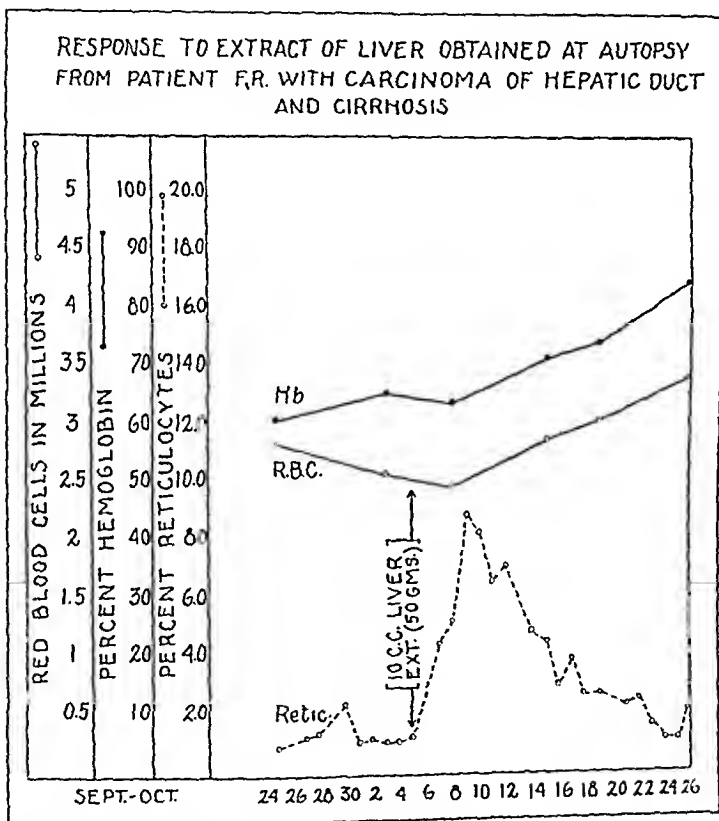


FIG. 4.

CASE 4. Extract from J. B. (No. 24540), patient with chronic passive congestion of the liver. The patient, a white male, aged 74, was admitted to the medical service of this hospital on December 8, 1935, with acute congestive heart failure. He had had symptoms of cardiac weakness for about 3 years and had been admitted 1½ years before with congestive heart failure, which was felt to be due to arteriosclerotic hypertensive heart disease with auricular fibrillation. At that time, he remained in the hospital for 2 weeks; signs of congestive failure including an enlarged tender liver were present. During the present admission which was of only 2 hours'

duration, there was no visible icterus, hemoglobin was 70% (Sahli) and the red cells numbered 3.9 millions. An M.C.V. determination was not done.

Necropsy (performed 12 hours after death) showed the presence of a typical nutmeg liver weighing 1805 gm., which on microscopic section showed central necrosis with hemorrhage. There was extensive generalized arteriosclerosis. An extract prepared from this liver was administered to a patient with pernicious anemia and cystitis with an effect as shown in Fig. 5. The presence of cystitis might have prevented the development of a more marked reticulocytosis, although the patient eventually had a complete remission.

RESPONSE TO EXTRACT OF LIVER OBTAINED AT AUTOPSY FROM
PATIENT J.B. WITH CHRONIC PASSIVE CONGESTION OF LIVER

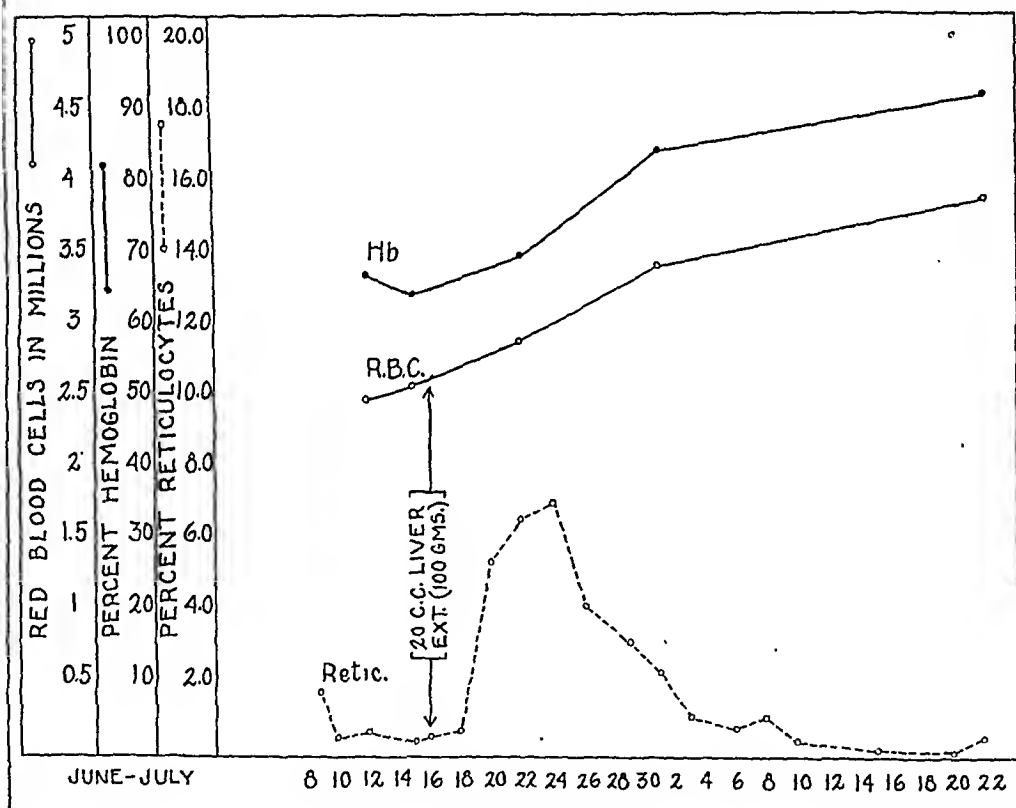


Fig. 5.

CASE 5. *Extract from H. P. (No. 46891), patient with chronic myeloid leukemia.* The patient, a white male, aged 70, was admitted to the medical service of this hospital on October 22, 1935. He complained of increasing weakness and dizziness for 2 to 3 years with marked pallor for over 1 year. Dyspnea and ankle edema had been present for 6 months. In addition to marked pallor slight fever was present. The abdomen was distended due to ascites. The liver was felt one fingerbreadth below the right costal margin and the spleen extended halfway to the left iliac crest. The white cells numbered 500,000 per c.mm. and the blood smear was typical of myeloid leukemia. The hemoglobin was 45% (Sahli) and the red cells

numbered 2.7 millions. An M.C.V. was not done. The patient died of bronchopneumonia 14 days after admission.

Necropsy was performed 3 hours after death. The liver which weighed 3480 gm. was described as large, moderately firm, and pinkish yellow. Microscopic sections revealed extensive leukemic infiltration. An extract prepared from it was administered to a patient with the result as noted in Fig. 6.

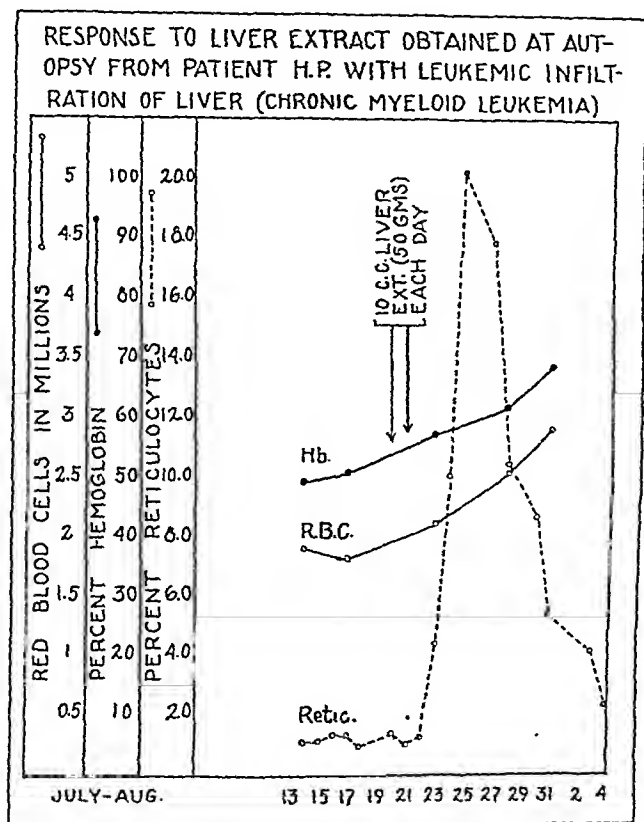


FIG. 6.

Summary. Extracts were prepared from the livers obtained post-mortem from 5 patients with chronic liver disease. These included 2 examples of portal cirrhosis, 1 of obstructive cirrhosis secondary to neoplasm of the hepatic duct, 1 of chronic passive congestion and 1 of extensive leukemic infiltration. The extracts were administered intramuscularly to a suitably controlled group of patients with pernicious anemia in relapse. A characteristic reticulocytosis resulted, followed by an increase in hemoglobin and red cell count and by marked clinical improvement.

The 3 patients with cirrhosis presented a macrocytic anemia, while the type of anemia in the remaining 2 patients was not definitely determined.

Conclusion. The human liver may contain the specific hemato-poietic principle even when it is the seat of extensive and protracted disease. This holds true even in the presence of macrocytic anemia.

This strongly suggests that the macrocytic anemia associated with liver disease is not caused by failure of the liver to store the specific anti-anemic substance.

We wish to express our appreciation to Dr. Ralph H. Fuller, of the Department of Pathology for his coöperation in this study.

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A CONSIDERATION OF THE PHENOMENON OF PURPURA FOLLOWING SCARLET FEVER.

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SEVERE purpura during the course of scarlet fever or following in its wake, has been a rare phenomenon in our experience. During the past 13 years only 2 cases of severe purpura were observed in very nearly 12,000 scarlet fever patients. Two other incidents of mild purpura have been studied. These occurred in individuals who had recently passed through a bout of scarlet fever, the purpura appearing after the termination of quarantine.

The literature contains about 50 reported cases of severe purpura occurring during the course of, or as a sequel to, scarlet fever. The rarity of the condition, therefore, warrants presentation of other cases and a discussion of the significance of this clinical entity.

We have had only two opportunities to perform necropsies on cases of scarlet fever with purpura. These 2 cases are not detailed in this series, as we do not have sufficiently accurate clinical data. In both of these the skin and viscera exhibited purpuric manifestations of a fine discrete type. The distribution of the purpura was most marked on the serous membranes, but also occurred in the bladder and intestinal tract. The significant feature of these 2 cases is that carefully performed postmortem cultures did not disclose streptococci in the blood or in these purpuric lesions. They were reported to us as of about 2 weeks' duration and of a fulminating type. The immediate cause of death in these cases was attributed

to severe toxemia, as there were no other significant anatomic features to which death could be attributed.

The essential gross lesions found in these cases were: A diffuse congestion of the lungs; a rather extensive pleural ecchymosis and purpura; cloudy softening of the myocardium with few fine discrete purpuric spots on the epicardium and at the base of the mitral valve; hyperplasia and swelling of the mesenteric and mediastinal lymph nodes; moderate hemorrhagic engorgement and hyperplasia of the spleen; a moist and pale liver; fine petechiæ in the gastric and intestinal mucosa, chiefly in the upper portions of the intestinal tract; moderate swelling and congestion of the kidneys without purpura; purpura in the bladder mucosa; and discrete, scattered, purpuric spots on the skin of the lower extremities. The diagnosis of scarlet fever was based upon antemortem findings and cultures from the throat. Microscopy disclosed considerable, generalized, parenchymatous swelling. The purpuric areas were not associated with thrombosis, but consisted of minute extravasations of blood, frequently perineural in distribution and often confluent to form large hemorrhages. The kidneys were not remarkable.

The following data are concerned with our clinical observations:

Clinical Abstracts. CASE 1.—A white girl, aged 13, entered the Milwaukee City Hospital for Contagious Diseases on February 11, 1937, with a history of sore throat and vomiting of 3 days' duration. On the fifth day of the disease a generalized rash appeared. The physical examination disclosed a typical strawberry tongue, injected pharynx, and a scarlet fever erythema of the skin. The temperature was 100.6°, the pulse 94 and the respirations 23 per minute. The blanching test was positive. Urinalysis did not disclose any abnormal constituents. A diagnosis of scarlet fever appeared warranted. The past medical history was entirely negative except for chicken-pox and measles. In particular, there was absence of a personal or familial history of evidences of hemorrhagic diatheses.

On the sixth day in hospital the temperature, which had been moderately elevated, returned to normal. On that day vaccination was performed. Two days prior to this there had been a moderate cervical adenitis which was now disappearing. On the tenth day in hospital stomach cramps developed, and there was a mild febrile reaction. There now appeared numerous discrete purpuric spots on the ventral surfaces of the lower extremities. The following day there was blood-tinged vomiting and more abdominal cramps. Tenderness and pain in the epigastrium developed. Large purpuric hemorrhages around the elbows and fresh crops of petechial spots over the lower extremities made their appearance on the 12th to the 14th day of the illness. Leukocyte count: 23,800 per c.mm. No hematuria. The hemorrhage in the skin continued to spread, involving the trunk and extremities, and also appeared in the conjunctivæ, scleræ, and palate. A diagnosis of Henoch-Schönlein purpura was made. Glucose and saline were administered by vein along with 80 cc. of convalescent serum. Three days after the appearance of the purpura the phenomenon was widely distributed. A whole blood transfusion was given. A blood platelet count at this time, namely, the 14th day in hospital and the 4th day of the purpura, was 300,000 per c.mm. Coagulation time and bleeding time were normal. The clot retraction was adequate. Nausea and vomiting continued along with fresh purpuric manifestations. On the 5th day of the purpura 0.2 cc.

of a 1/3000 dilution of moccasin snake venom was given subcutaneously. The following day this was increased to 0.4 cc. At this time the purpura of the face, palate, and uvula was so intense as to warrant the use of the term "infarction." Blood transfusion was repeated.

On the 8th day of the purpura the urine was quite bloody. Snake venom was increased to 0.8 cc. New purpuric areas did not appear after the 8th day of the condition. Hematuria disappeared within a day or two, although albuminuria persisted for several days. She was transferred to another institution 31 days after admission to the fever hospital. The clinical course after this was that of progressive improvement with gradual disappearance of the purpura, and at the present writing this patient has entirely recovered and does not present any abnormalities in the blood nor any evidences of purpura, even after the application of the tourniquet test. Figures 1, 2, 3, 4, and 5 are indicative of the distribution and extent of the purpura.

CASE 2.—A white female, aged 18, was admitted to the hospital January 1, 1935, having had a sore throat and vomiting for 4 days. The tongue was typically strawberry. There was an injected pharynx and enlarged cervical lymph nodes. On the day after admission to the hospital uterine bleeding began and continued for 20 days, during which time the erythrocytes in the blood were reduced to 2,640,000 per c.mm. During the period of uterine bleeding widely distributed purpuric spots, over the lower extremities, in particular, developed. On the 22d day in hospital the patient was transferred to another hospital and was given a blood transfusion. She was discharged from that hospital on February 10, 1935, free of purpura and apparently entirely well. During this period she was given moccasin snake venom once. The blood of this patient showed anemia. The platelets ranged from 190,000 to 250,000 per c.mm., the leukocytes from 5000 to 6100 per c.mm., the bleeding time, coagulation time, and clot retraction were all entirely normal.

CASE 3.—A white female, aged 22, had a mild attack of scarlet fever in 1933. After discharge from the hospital irregular uterine bleeding developed, and shortly after, within a few weeks, recurrent crops of petechiae in the skin, particularly on the lower extremities appeared. Hemorrhages occurred in the skin upon the slightest traumatic provocation. This condition continued for about a year, during which time there were occasional attacks of hematuria, associated with renal colic. Blood transfusions were performed on 3 occasions. In the latter part of 1935 there was a moderate degree of anemia. The hemoglobin was 13.5 gm. The blood platelets were entirely within normal limits. Bleeding time, coagulation time, and clot retraction were normal. There was a slightly purpuric manifestation, chiefly on the lower extremities. The urine contained a few blood cells. The tourniquet tests were weakly positive. Recurrent abdominal pain, mostly in the right lower quadrant, was a rather prominent feature. Snake venom therapy was started, but each injection was followed by severe local reaction and purpura, and after 6 attempts this therapy was discontinued. The patient was again observed in the latter part of 1936, at which time all signs of purpura had been absent for several months, and the condition seemed to be entirely relieved. Menstruation was normal, and there was complete relief from all previous complaints.

CASE 4.—An 11-year-old boy developed scarlet fever in June, 1937. One week after discharge from quarantine purpura developed which involved the skin and mucous membranes of the mouth. At this time mild hematuria was detected. Fresh crops of purpura appeared daily for 4 days. A blood examination disclosed a mild anemia. After the 4th day of purpura, following a blood transfusion, the condition subsided, and in September, 1937, the boy appeared entirely well without any evidence of purpura and without any evidences of nephritis.

Comment. The purpuric manifestations in these cases were apparent chiefly in the skin, although the mucous membranes in 2



FIG. 1

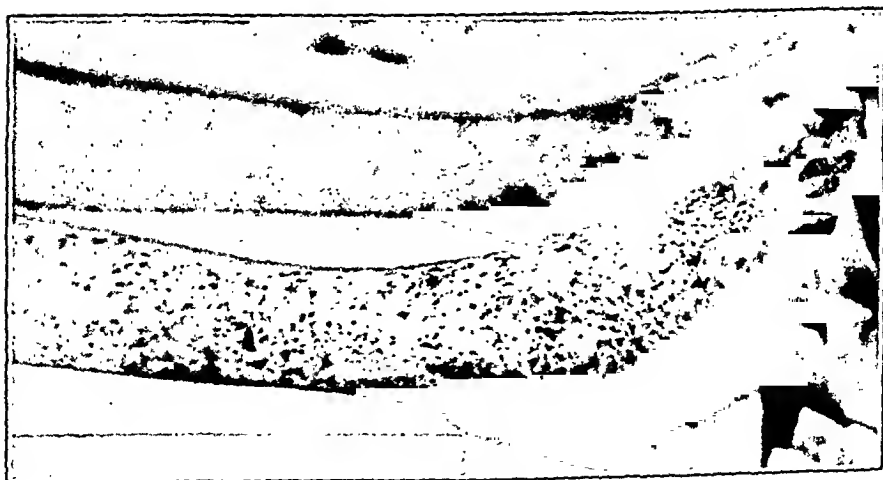


FIG. 2

of the cases were also involved. In the first case, the hemorrhages became confluent, and local infarctions resulted. Distribution over



FIG. 3



FIG. 4



FIGS. 1, 2, 3, 4 and 5.—Purpuric lesions. Case 1.

the bony prominences was a feature of this case. Prominent in all cases was the absence of detectable enlargement of the spleen or liver. In none of these cases was there any evidence of previous hemorrhagic tendencies or of familial hemorrhagic characteristics. Associated with the purpura was hematuria in all of these incidents. The hematuria disappeared with the purpura and appeared to be a part of the hemorrhagic episode. None of these cases was followed by evidences of nephritis. It would appear, then, that hematuria in scarlet fever may be a purpuric phenomenon and that in the absence of evidences of kidney damage, hematuria by itself is not evidence of scarlet fever nephritis.

Scarlet fever toxin appears to have a strong effect upon capillary endothelium. Thus, the toxin injected into the skin produces erythema, in which evidences of capillary fragility and damaged endothelium appear. This phenomenon occurs in the vascular endothelium of the glomerular tufts. The hematologic findings in our cases would seem to be of little significance so far as positive data are concerned. Except for the anemia, which responded rapidly, there was not any evidence of toxic depression of the bone marrow. Thrombocytopenia reported by others, was not a feature of our cases. Leukocytosis was not striking in our cases, although it has been reported by others.

Treatment by blood transfusion and snake venom seems to be indicated. The use of snake venom in acute nephritis has been suggested by Peck and Baehr. Snake venom was found by Peck⁸ to inhibit the Schwartzman reaction, and because of the hemorrhagic features of this reaction, the use of snake venom was suggested as a means of increasing capillary resistance to the streptococcic toxin. In our experience, the value of snake venom in this condition is not established, but its use should be encouraged. Blood transfusions likewise seem beneficial. Splenectomy and Roentgen ray therapy, reported by others, seems to us unsound.

Stevenson,¹⁵ in 1912, was able to find only 33 cases of purpura in scarlet fever. McConnell and Weaver,⁷ in 1922, found about 50 cases of purpura hemorrhagica and of purpura fulminans associated with scarlet fever. In 1933, Box² was able to find about 50 cases recorded.

The clinical features of purpura in scarlet fever will depend upon the severity of the process. In the fulminating type the hemorrhages develop and spread rapidly. Confluence is a prominent feature. Skin and viscera are severely involved. Distribution over bony prominences is striking. The lesions may exhibit dark to black discoloration, infarction and necrosis may follow. Hemorrhages from the nose, pharynx, bowel, bladder, and kidney are to be expected. Hemorrhages into joint cavities did not occur in our cases. The spleen and liver were not enlarged. Fever is variable and may be severe. In the milder cases the hemorrhages are finer, more dis-

crete, and less apt to be confluent. Skin and visceral surfaces are involved, and the condition may become subacute or chronic and intermittent.

Hematuria is a feature of both types. The urinary sediment does not contain evidences of renal parenchymal irritation. The entire course of the hematuria and its disappearance with the subsidence of the purpura indicated rather strongly that the capillary endothelium in the kidneys has been rendered permeable as a result of the direct action of the scarlet fever toxin. As previously mentioned, scarlet fever toxin produces changes in capillary endothelium (Smith¹⁴). In the areas of erythema, produced by injecting the toxin, Birkhaug has demonstrated swelling of these cells. In early glomerulonephritis the lesions are distinctly capillary and vascular. In this form of purpura it seems likely that the lesions develop as a result of a toxic endotheliosis, although this term should not be taken to imply that capillary endothelium, sensitized by the toxin, proliferates as in other forms of endotheliosis.

TABLE 1.—REVIEW OF BLOOD COUNTS IN SCARLATINAL PURPURA.*

	Day of disease.	Red cells (milli.).	Hemoglobin, %.	Platelets (thous.).	White cells (thous.).	Neutrophils, %.	Lymphocytes, %.	Monocytes, %.	Myelocytes, %.	Eosinophils, %.	Basophils, %.	Remarks.
Biernacki and Dykes	8th week	3.6	50.0	85	10	2	..	
Elliott	19th day	2.3	..	Not incr.	65.4	79	13	..	5.2	5	..	3 nucleated red cells
Risel	16th day	5.2	..	Not incr.	38.1	83.3	10.4	..	2.1	..	2.1	3 nucleated red cells
Rollston and McCirick	10th day	1.8	..	Not incr.	57.6	63.4	6.3	Many microcytes
McCirick	18th day	3.7	..	Not incr.	15.7	86	2.5	
Prior	22d day	5.6	..	300	4.0	83	15	1.5	..	0.0	..	Coag. time, 4 mins.
Gibson and Hobson	16th day	4.9	..	Large numbers	27.3	71	21	8	
Wood-Smith	16th day	5.4	80	163	6.4	61	30	8	1	Platelets, 378,000 3 mos. later
Box and Massing- ham	13th day	3.4	65	0 in 4000 R.B.C.	39.8	81.5	14	2	2.5	
Prior	23d day	4.5	64	146 (some very large)	21.9	77	L.4 S.11 .5	4	..	3	..	Transitionals, 0.5%
Prendergast	40th day	4.5	55	None seen	20.4	50	32	2	..	Transitionals 4%
Box	5th week	2.9	40	93	22.1	66	26	6	..	2	..	Few nucleated red cells; polychroma- sia
Fox and Enzer (Case 1)	11th day	4.1	92	367	23.6	78	11	7	3.5	0.5	..	Coag. time, 4 min.; bleed time, 5 min.; sed. rate, normal
Fox and Enzer (Case 2)	7th day	2.6	48	154	5.0	56	27	3	5	7	2	Poikilocytosis; ani- soeytosis; micro- cytes; bleed. time, 1.5 min.; coag. time, 1 min.

* Most of the data in this table are taken from the article by Box,² in which the differential counts did not always add up to 100%.

A study of the reported cases discloses rather incomplete hematologic investigations. Table 1 summarizes the available literature on the subject and includes data from Cases 1 and 2 reported here.

In our cases, thrombocytopenia did not occur. There was a moderate to severe acute anemia, and leukocytosis may occur. The stained smears did not give any evidence of significant bone marrow activity.

Treatment of the condition can hardly be said, at the present time, to be entirely specific or even well-founded. We found transfusions, and, we believe, snake venom to be helpful and perhaps effective. However, spontaneous recovery is also a possibility, particularly in the milder cases. The effectiveness of transfusion is probably based upon a desensitization of the capillary endothelium, or perhaps its past results are due to increase in capillary "resistance." Peck and Schneierson¹⁰ showed that moccasin venom did not prevent the development of nephritis in scarlet fever, but also it did not damage the renal capillaries. Since the glomerulonephritis is essentially a vascular phenomenon, Baehr suggested the use of venom to inhibit the development of the lesion, much in the manner that venom inhibits or prevents the Shwartzman phenomenon. It was from that point of view that the venom was used in this case. The use of venom in purpura has been reported by several authors, notably, Rosenthal and Peck.⁹ We hold no brief for the use of venom in these cases, but suggest it be given a trial early in the condition.

Splenectomy has been suggested by several authors, notably, Pemberton,¹¹ Askey and Toland,¹ Brown and Elliott,³ and Pollok.¹² Jones and Tocantins⁵ suggest the use of whole blood transfusion. Rudisill¹³ reports the successful use of Roentgen ray irradiation of the spleen. Klima⁶ recommends Tryphman (adrenals); and Greenwald,⁴ snake venom. To us splenectomy and irradiation seem decidedly contraindicated.

In the final analysis, this type of purpura appears to be due to an allergic or hypersensitive state to a specific protein agent. Treatment should be directed to minimizing the allergy (increased resistance) or neutralizing the antigen.

Summary. Purpura in severe and mild forms occurs rarely in scarlet fever. Thrombocytopenia does not appear to be a factor in the production of the purpura. Purpura did not occur in the reported cases prior to the scarlet fever. Sensitization of the capillary endothelium by the scarlet fever toxin affords a reasonable explanation for the purpura, since the scarlet fever toxin strongly affects capillary endothelium. Hematuria in scarlet fever, in the absence of other evidence of nephritis, is probably an expression of the effect of the scarlet fever toxin on the glomerular endothelium, and in that sense, is indicative of renal purpura. Hematuria, therefore, is not necessarily evidence of nephritis.

The literature on the subject is reviewed and in this report 4 instances of purpura following non-fatal scarlet fever are described. The postmortem findings in 2 other instances are briefly reviewed.

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CHRONIC LEUKEMIA.

A STUDY OF THE INCIDENCE AND FACTORS INFLUENCING
THE DURATION OF LIFE.

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THE medical literature contains little data relating to the incidence of leukemia. This study of the records of patients suffering from leukemia in several large general hospitals located in New York, Boston, and Philadelphia* has provided additional information not only with regard to the incidence but also concerning the significance of certain prognostic signs.

The Variation in the Incidence of Leukemia Since 1904. Wollstein and Bartlett¹⁷ (1925) reported 15 instances of acute leukemia among 25,246 admissions to the Babies' Hospital in New York City. Hoffman and Craver⁴ (1931) state that myelogenous leukemia makes up only 0.4% of the patients seen at Memorial Hospital in New York City. Ordway and Gorham¹² state that 1 case of leukemia occurs among every 1000 hospital admissions. Ikeda⁶ (1931) found 77 cases of leukemia in the records of 12,396 necropsies at the University of Minnesota Hospital from 1900 to 1928 inclusive. Nielsen¹¹ (1932) reported that in Denmark the annual death rate from leukemia was roughly 1 per 50,000 population, the figure being based on an examination of death certificates for the period 1923-1932. The first two of these reports are not from general hospitals.

The autopsy records of the Boston City, Massachusetts General, and the New York Hospitals from 1905 to 1934 were studied in an effort to determine if there had been any change in incidence during that 30-year period.

* We are grateful to the Boston City, the Children's (Boston), the Massachusetts General, and the University of Pennsylvania Hospitals for permission to make use of their records.

Cases of acute and chronic myelogenous, lymphogenous, and monocytic leukemia were included.* Instances in which the diagnosis was questionable and cases of lymphosarcoma were not included. Because of the fact that at the New York Hospital, autopsies on stillbirths and individuals less than 10 years of age accounted for only 5% of the necropsies prior to 1932 and 50% of the total since 1932, all autopsies on persons 10 years of age and under have been excluded from this hospital's series. The results are presented in Table 1.

TABLE 1.—THE INCIDENCE OF LEUKEMIA—AUTOPSIES.

Years.	<i>Boston City Hospital.</i>		<i>Mass. Gen. Hospital.</i>		<i>New York Hospital.</i>	
	No. of autopsies.	Cases of leukemia.	No. of autopsies.	Cases of leukemia.	No. of autopsies.	Cases of leukemia.
1925-34	4909	41 (0.8%)	2793	59 (2.0%)	1622	18 (1.1%)
1915-24	1865	10 (0.5%)	1360	19 (1.4%)	915	7 (0.78%)
1905-14	1601	8 (0.5%)	2231	19 (0.9%)	1003	5 (0.5%)
Totals	8375	59	6384	97	3540	30

Although the incidence of leukemia at necropsy differed in the hospitals studied, in each instance both the percentage of leukemia cases and the number of leukemia cases have increased with each succeeding decade. The significance of this increase at autopsy cannot be determined because the result obtained in a study of this kind is affected by so many factors that cannot be measured or estimated accurately, such as the improvement in the diagnosis of leukemia by the practising physician, the percentage of such patients in the community that were hospitalized, the incidence in all the other hospitals in the community during the same period, the policy of the hospital about admitting certain types of disease, the presence or absence of a staff member especially interested in leukemia, the decreasing number of deaths from other causes.

The incidence of leukemia based on clinical diagnoses and hospital admissions at The Children's (Boston), Massachusetts General, and the University of Pennsylvania Hospitals is shown in Table 2. Only the first admission of the leukemia patient was counted. The figures for the different hospitals cannot be compared, because the figure for "number of admissions" does not have the same significance at all the institutions. At the Children's Hospital (Boston) it includes only ward and private medical patients, at the Massachusetts General Hospital only the medical and surgical patients admitted to the public wards, while at the University of Pennsylvania Hospital it includes all admissions on all services, private room, and public ward.

Prognostic Factors. Most writers on the subject^{2,7,12,13,16} state that a decline in the general condition of the patient, increasing

* They have been grouped rather than tabulated according to the predominating type of cell because of the relatively small number of cases in most of the periods studied.

anemia, increasing percentage of blast cells, increasing leukocyte count, and the manifestation of a bleeding tendency indicate an unfavorable course and progression of the disease. While the correctness of these prognostic signs in a majority of instances is established by clinical experience, in the literature there are few records of attempts to evaluate the accuracy of these guides by the study of a group of cases. The purpose of the second part of this communication is to present the results of such a study in order to determine the relationship of several of these factors to the duration of life.

TABLE 2.—INCIDENCE OF LEUKEMIA: CLINICAL DIAGNOSES.

Children's Hospital, Boston.

Years.	No. of thousand admissions.	No. of leukemia cases.	Leukemia per 1000 admissions.	
			5-year period.	10-year period.
1930-1934	5.52	46	8.3	
1925-1929	4.98	31	6.3	
				7.3

Massachusetts General Hospital.

1930-1934	38.7	79	2.0	
1925-1929	36.5	43	1.2	
				1.6
1920-1924	32.8	58	1.5	
1915-1919	24.0	15	0.6	
				1.05

University of Pennsylvania Hospital.

1930-1934	48.6	34	0.64	
1925-1929	49.1	28	0.57	
				0.60
1920-1924	40.1	21	0.52	
1915-1919	20.9	13	0.62	
				0.57

Material. The records of 478 cases of leukemia at The Children's (Boston), Massachusetts General, New York, and the University of Pennsylvania Hospitals have been studied. The great majority of these patients were admitted between the years 1925-1936, the remainder between 1917-1925. In the group of 478, there were 180 cases of chronic myelogenous leukemia and 128 of chronic lymphogenous leukemia. In 87 patients with chronic myelogenous leukemia and 49 patients with chronic lymphogenous leukemia the duration of life after the onset of symptoms apparently due to leukemia is known. These 136 cases form the material for the second part of this communication.

Only cases of chronic leukemia are included in this study. Regardless of the age at onset, no cases with a total duration from the onset of symptoms to death of less than 6 months have been included, and no records of individuals less than 15 years of age at the time of onset have been included. Practically all these patients were treated by irradiation, arsenic, transfusion, or a combination of these agents.

Age Incidence. The age incidence of the 180 individuals with chronic myelogenous leukemia and of the smaller group of 87 in whom the total duration of the disease is known was similar to that reported by Ward,¹⁵ 1917 (247 cases), Minot, Buckman and Isaacs,¹⁰ 1924 (166 cases), Hoffman and Craver,⁴ 1931 (80 cases), and Rosen-

thal and Harris,¹⁴ 1935 (104 cases), the greatest number occurring between the ages of 35 and 45.

The age incidence of the 128 patients with chronic lymphogenous leukemia, and the smaller group of 49 considered in more detail, was similar to that reported by Ward,¹⁵ 1917 (84 cases), Minot and Isaacs,⁹ 1924 (92 cases), and Rosenthal and Harris,¹⁴ 1935 (104 cases), the greatest number occurring between the ages of 45 and 55.

Sex Incidence. Of the 180 cases of chronic myelogenous leukemia, 108 (60%) were males and 72 (40%) were females. Of the 87 patients in whom the total duration of the disease is known, 46 (53%) were males and 41 (47%) were females. Minot, Buckman and Isaacs,¹⁰ 1924, found that in 605 cases, including their own and those reported by Cabot, Vogel, Ward, Giffen and Lazarus, 60% were males and 40% were females. In Hoffman's and Craver's series of 82 cases,⁴ 1931, 68% were males and 32% were females.

Of the 128 individuals in this series having chronic lymphogenous leukemia, 72% were males and 28% were females. Of the 49 in whom the total duration of the disease is known, 36 (72%) were males and 13 (28%) were females. Ward,¹⁵ 1917, reported that 75% of 84 cases of chronic lymphogenous leukemia were males and Minot and Isaacs,⁹ 1924, reported that 74% of 92 cases were males.

Duration of Life. Minot, Buckman, and Isaacs¹⁰ (1924) found the average duration of life after onset of symptoms to be 3.5 years in 78 patients with chronic myelogenous leukemia treated by irradiation, 3.04 years in 52 patients not treated by irradiation. About 10% died in the first year, 42% lived from 2 to 4 years, and 12% survived more than 5 years. Hoffman and Craver⁴ (1931) found the average duration of life after onset of symptoms to be 3.36 years in 71 patients with chronic myelogenous leukemia treated by irradiation. Arendt and Gloor¹ (1932) reported that the average duration of life after onset of symptoms was slightly over 4 years in their 39 patients with chronic myelogenous leukemia treated by Roentgen ray and arsenic. Rosenthal and Harris¹⁴ (1935) reported that of 157 patients with chronic myelogenous leukemia, 35% died between the fourth and twelfth month, 45% lived from 2 to 4 years, a few survived from 5 to 11 years. In 104 cases of chronic lymphogenous leukemia they found the duration of life to be essentially the same. Minot and Isaacs⁹ (1924) found the average duration of life after onset of symptoms in 80 patients with chronic lymphogenous leukemia over 30 years of age to be 3.45 years, the average being the same in irradiated and non-irradiated patients. About 60% lived from 1 to 4 years, 14% from 6 to 8 years.

Chart 1 represents the percentage of the present series surviving at each year after onset. The average duration of life after onset of symptoms was 3.2 years for the group with chronic myelogenous leukemia and 3.6 years for the group with chronic lymphogenous

leukemia. The individual variations were from 6 months to 16 years in each type.

Although this series of 87 cases of chronic myelogenous leukemia and 49 cases of chronic lymphogenous leukemia is a small one, because the age distribution, sex distribution, and duration of life are the same as those reported in much larger series, this group is thought to be a typical one.

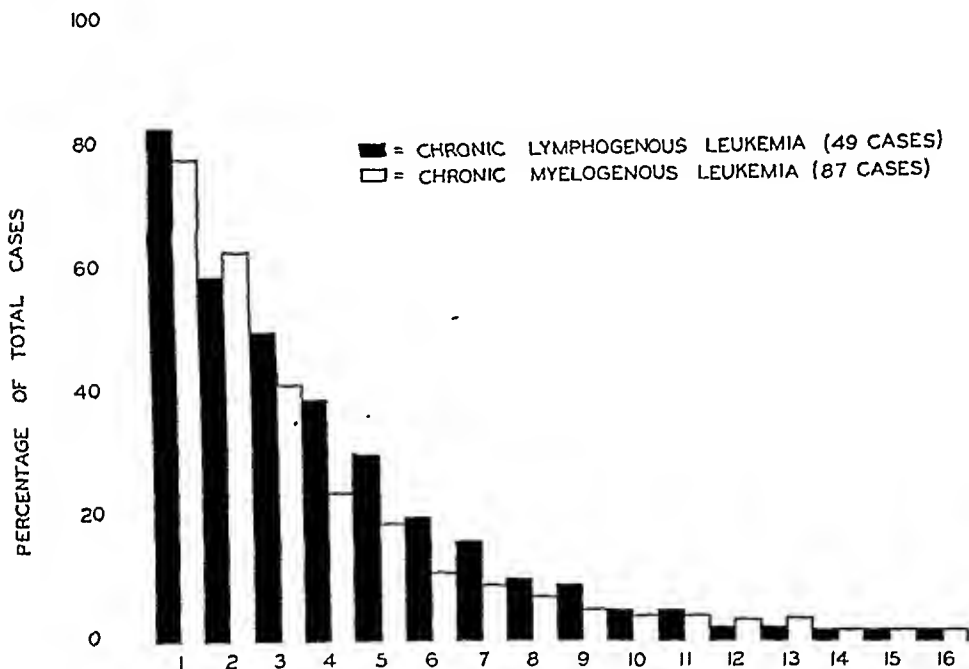


CHART I - DURATION OF LIFE AFTER ONSET OF SYMPTOMS (YEARS)

Relation of Age at Onset to Duration of Life. Minot, Buckman and Isaacs¹⁰ (1924) and Hoffman and Craver⁴ (1931) thought that the age at which chronic myelogenous leukemia appeared did not greatly influence its duration. Minot and Isaacs⁹ (1924) stated that chronic lymphogenous leukemia lasted a shorter time in younger persons than in older persons, but their series included only 7 individuals less than 30 years of age.

Table 3 gives information concerning the duration of life after the onset of symptoms in the two type of cases in this series. The age groups that vary from the average of the entire group with chronic myelogenous leukemia are the young and old, but there are probably too few cases for the results to be significant. Individuals developing symptoms from lymphogenous leukemia between the ages of 40 and 60 averaged a longer course than the others.

Relation of Anemia to the Duration of Life. Marked anemia or increasing anemia is accepted generally as an unfavorable sign, Forkner,² Whitby and Britton,¹⁶ Kracke and Garver,⁷ Pepper and

Farley.¹³ Well recognized but little emphasized is the difference of the significance of anemia in the two types of leukemia under consideration. Minot and Isaacs⁹ (1924) state that in cases of chronic lymphogenous leukemia with hemoglobin of 50% or below, it is rare to see much symptomatic improvement as the result of therapy in contrast to the distinct benefit often seen in cases of chronic myelogenous leukemia having marked reduction in hemoglobin. Forkner² states that severe anemia is more serious in patients with chronic lymphogenous leukemia than in those with chronic myelogenous leukemia.

TABLE 3.—CHRONIC MYELOGENOUS AND CHRONIC LYMPHOGENOUS LEUKEMIA, AGE OF ONSET OF SYMPTOMS, AND AVERAGE DURATION OF LIFE AFTER ONSET OF SYMPTOMS.

Chronic myelogenous leukemia.		Age by decades.	Chronic lymphogenous leukemia.	
Average duration of life (yrs.).	No. of cases.		Average duration of life (yrs.).	No. of cases.
1.0	2	10-19	1.0	2
1.5	9	20-29	3.0	3
4.4 } *3.3 }	25 } *21 }	30-39	3.0	4
3.3	23	40-49	4.5	9
3.0	20	50-59	4.5	19
3.3	6	60-69	2.1	11
0.7	2	70-79	4.0	1
3.2	87	Totals	3.6	49

* Excluding the 4 cases living more than 10 years, all of which occurred in this decade.

In this series, cases of both types of leukemia have been divided into three groups, those surviving less than 1 year, those surviving 1 to 3 years, and those surviving more than 3 years. They also have been divided into three groups according to the degree of anemia: those with marked anemia (hemoglobin less than 50%), those with moderate anemia (hemoglobin 50 to 70%), and those with little or no anemia (hemoglobin over 70%). Hemoglobin values are those before treatment was given. They are recorded in per cent because factors for conversion into grams were not available in every instance and, even with slightly different standards, percentage values were considered satisfactory for the divisions employed. The duration of life is that after the hemoglobin determination and not after the onset of symptoms. This way of stating the duration of life was selected because this study is concerned mainly with the duration of life after the patient first consults a physician, and because only in exceptional instances could one learn the hemoglobin value at the time symptoms developed. The results are presented in Table 4.

In this series, the groups with marked anemia had a much shorter course than the other groups, and this was especially evident in

those with lymphogenous leukemia. No patient with either type of leukemia and a hemoglobin of 30% or less (12 cases) survived for as long as a year. That a marked anemia does not invariably indicate an unusually short course is shown by the fact that of the 35 patients with chronic myelogenous leukemia who had hemoglobin values of between 30 and 50%, 12 survived for more than 1 year, 3 for more than 3 years. One patient with chronic lymphogenous leukemia who had a hemoglobin reading of 45% lived for 16 years after coming under observation.

TABLE 4.—CHRONIC MYELOGENOUS AND CHRONIC LYMPHOGENOUS LEUKEMIA, HEMOGLOBIN (%) AND PERIOD OF SURVIVAL.

Chronic Myelogenous Leukemia.

Initial hemoglobin (%)	No. of cases living less than 1 year.	No. of cases living 1-3 years.	No. of cases living more than 3 years.	Totals.
20-49	23	9	3	35
50-69	16	16	6	38
70-100	2	5	7	14
Totals	41	30	16	87

Chronic Lymphogenous Leukemia.

20-49	12	0	1	13
50-69	8	6	1	15
70-100	8	7	6	21
Totals	28	13	8	49

Relation of Leukocyte Count to Duration of Life. The total leukocyte count is considered one of the less reliable prognostic signs. Its tendency in some patients to rise abruptly and in others to drop steadily just before death is well known. That in some instances it varies greatly and in others only slightly, with and without treatment, and frequently fails to parallel the clinical course of the patient is also well known. These are probably some of the factors responsible for the different opinions that have been expressed regarding its interpretation.

Kracke and Garver⁷ (1937) quote Naegeli as saying that patients with chronic myelogenous leukemia and high leukocyte counts succumb earlier than those with low leukocyte counts. With reference to lymphogenous leukemia, they state that the higher the leukocyte count the more unfavorable the prognosis. Rosenthal and Harris¹⁴ (1935) found that the majority of their patients with chronic myelogenous leukemia with leukocyte counts of 15,000 per c.mm. or less died within 1 year. Hunter⁵ (1937) states that patients with chronic myelogenous leukemia and low leukocyte counts have a more rapid course than those with higher counts.

Cases of both types of leukemia in the present series are tabulated according to periods of survival and total leukocyte counts as shown in Table 5. The leukocyte count in each instance is the initial

count before treatment, the period of survival is that after the leukocyte count, not after the onset of symptoms.

TABLE 5.—CHRONIC MYELOGENOUS AND CHRONIC LYMPHOGENOUS LEUKEMIA:
LEUKOCYTE COUNT AND PERIOD OF SURVIVAL.

<i>Chronic Myelogenous Leukemia.</i>				
Initial leukocyte count.	No. of cases living less than 1 year.	No. of cases living 1-3 years.	No. of cases living more than 3 years.	Total.
3,000-39,000	15	0	1	16
40,000-300,000	15	19	13	47
301,000-750,000	11	11	2	24
Totals	41	30	16	87
<i>Chronic Lymphogenous Leukemia.</i>				
3,000-39,000	11	5	5	21
40,000-300,000	13	5	3	21
301,000-750,000	4	3	0	7
Totals	28	13	8	49

In this series, the group of patients having myelogenous leukemia and a leukocyte count of less than 40,000 per c.mm. had a much shorter course than the other groups. A relatively low leukocyte count was a more reliable sign of an early fatal outcome than a high leukocyte count was of a more favorable outlook. Of the 16 patients with myelogenous leukemia having leukocyte counts of less than 40,000 per c.mm., 13 had hemoglobin values of less than 50%; not one of these 13 individuals survived for as long as 1 year. The group with chronic lymphogenous leukemia having lower counts fared slightly better than the groups with the higher counts.

In view of the decrease in leukocyte count that usually accompanies improvement during therapy, it was somewhat surprising to find that in this series the untreated patients with myelogenous leukemia having lower leukocyte counts apparently lived a shorter time than those with higher counts. Other explanations for the difference in the expectancy of life after diagnosis were considered. One possibility is that the small group of patients with the lower leukocyte counts might have had symptoms for a longer time before consulting a physician than those with higher counts.

The average duration of symptoms before and after diagnosis in the patients with myelogenous leukemia having counts less than 40,000 per c.mm. and in those with higher counts is shown in Table 6. That average values are misleading in this instance is shown by the fact that of the group of 16 with leukocyte counts of less than 40,000 per c.mm. only 1 individual lived even half as long after diagnosis as the average duration of life after diagnosis for the whole group. If the rare cases living more than 10 years are excluded from each group as shown in the second half of the table, the average duration of life after coming under observation is 0.7 years for the 15 cases with leukocyte counts of less than 40,000 per c.mm. and 1.4 years for

the 67 cases with higher leukocyte counts. The average duration of life after the onset of symptoms in the group with lower leukocyte counts is only 0.4 years less than the group with higher counts as the former apparently came under observation 0.3 years later in the course of the disease.

TABLE 6.—CHRONIC MYELOGENOUS LEUKEMIA: LEUKOCYTE COUNT AND DURATION OF DISEASE BEFORE AND AFTER DIAGNOSIS.

<i>All Cases.</i>				
Initial leukocyte count.	Average duration of life (yrs.).	Average duration of symptoms before diagnosis (yrs.).	Average duration of life after diagnosis (yrs.).	No. of cases.
Less than 40,000	3.2	1.3	1.9	16
More than 40,000	3.2	1.45	1.75	71
<i>Cases Living Less Than 10 Years.</i>				
Less than 40,000	2.0	1.3	0.7	15
More than 40,000	2.4	1.0	1.4	67

Relation of Bleeding Manifestations to the Duration of Life. Bleeding is one of the commonest manifestations of leukemia. That it occurs most frequently in advanced and acute cases and is a sign of an early termination of the disease is accepted generally.

Minot and Buckman⁸ (1924), in studying the course of the platelet count in 75 patients with chronic myelogenous leukemia and 50 patients with chronic lymphogenous leukemia, observed petechiæ in 50% of those with myelogenous leukemia. The petechiæ were always associated with thrombocytopenia, usually appeared towards the end of the disease, occasionally a few years before death. Evidence of bleeding other than petechiæ occurred in 25% of the patients. In chronic lymphogenous leukemia, bleeding in the form of ecchymoses and petechiæ was more common than in chronic myelogenous leukemia. Usually the bleeding was present only shortly before death. In 10%, however, it was found for as long as 1 year before death and sometimes for 2 years.

At the time of the first admission, a history of purpura, bleeding gums, epistaxis, hematemesis, melena, occurring alone or in combination was obtained in 18 (20%) of 87 patients with chronic myelogenous leukemia and in 8 (16%) of 49 patients with chronic lymphogenous leukemia. Of these 18 patients with myelogenous leukemia, 12 (66%) succumbed within 1 year after the appearance of bleeding, while with the 69 individuals with myelogenous leukemia giving no history of bleeding 29 (43%) died during the first year. Some of the patients included in the group of 69 developed bleeding before death, but in the study only the findings at the first visit were considered. Of the 6 patients with myelogenous leukemia giving a history of bleeding who survived for more than 1 year, 3 had hemoglobin values of less than 50%, all had leukocyte counts between 60,000 and 770,000 per c.mm., while of the 12 dying during

the first year, 9 had hemoglobin values of less than 50%, 9 had leukocyte counts of less than 40,000 per c.mm. Six individuals not included in the group of 18 patients with myelogenous leukemia and bleeding gave histories of excessive vaginal bleeding; all 6 survived more than 1 year, 3 for more than 3 years.

Of 8 subjects with lymphogenous leukemia giving a history of bleeding, 4 died during the first year, 4 lived from 1 to 2 years, none survived longer than 2 years. The number of cases is too small for the result to be significant.

The group of patients with chronic myelogenous leukemia with evidence of bleeding lived a shorter time after coming under observation than the group without bleeding. That some patients with myelogenous leukemia with bleeding manifestations may do well under treatment is shown by the survival of 4 individuals for more than 3 years. This improvement is less likely to occur if there is marked anemia, and rarely occurs if the leukocyte count is low.

Relation of Specific Skin Lesions to Prognosis. Specific lesions of the skin were proved by biopsy or autopsy in 9 of the 128 cases of chronic lymphogenous leukemia, in 1 of the 180 cases of chronic myelogenous leukemia. The average duration of life after the onset of symptoms in the 9 cases of lymphogenous leukemia with specific skin lesions was 3.5 years as compared with 3.45 years for the whole group of 49. The average duration of life after diagnosis was 1.0 year in the 9 cases with skin lesions and 1.6 years in the 40 cases without skin lesions. Only 1 case with skin lesions had a hemoglobin of less than 50%, all 9 had leukocyte counts between 55,000 and 600,000 per c.mm., 8 being over 90,000 per c.mm.

The duration of life in the individual with myelogenous leukemia and specific skin lesions is not known. Goldhamer and Barney³ (1936), reviewing 16 previously reported cases of myelogenous leukemia with skin manifestations and 1 of their own, found the duration of life after the appearance of skin lesions to vary from 11 days to 4 months, the average being 64 days.

Comment. In determining the incidence of leukemia, the acute leukemias and the different cell types were not grouped separately because in each period studied the total number of cases was so small that further subdivision seemed inadvisable.

A consideration of the relationship of the immature types of cells to the duration of life has not been included because different persons made the counts and used different classifications. Therefore, any conclusion that one might reach would not be justified. Basal metabolic rates, platelet counts, and values of the various clotting factors were not included because of insufficient data.

No conclusions could be drawn as to the benefit derived from transfusions in this series. In most instances, they were given to patients apparently in the advanced stages of the disease, having a poor immediate prognosis.

Discussion of the factors responsible for the anemia, bleeding, and variations in the leukocyte count is beyond the scope of this paper.

The prognostic factors considered are those that were present when the patient was first seen, and should enable one to give a more reliable estimation of the duration of life in certain types of cases. The subsequent course of the patient while under treatment is, of course, valuable in this estimation. The results also demonstrate that those individuals in whom the duration of the disease will be short are recognized more easily than those who will have the average duration of life or better, but that in exceptional instances a combination of unfavorable signs may be misleading.

In general, the results of the study confirm the prevailing clinical impression.

Summary and Conclusions. 1. The incidence of leukemia as determined from clinical records was 7.3 cases per 1000 admissions at the Children's Hospital, Boston, for the years 1925-1934. At the Massachusetts General Hospital there were 1.05 cases of leukemia per 1000 admissions for the period from 1915-1924, 1.6 cases per 1000 admissions from 1925-1934. At the University of Pennsylvania Hospital there were 0.57 cases of leukemia per 1000 admissions from 1915-1924, 0.60 cases per 1000 from 1925-1934.

2. The incidence of leukemia at autopsy at the Boston City Hospital, Massachusetts General Hospital, and the New York Hospital, was 0.8%, 2.0%, and 1.1% respectively for the period 1925-1934. This is an increase of from 60 to 100% over the 1905-1915 period in each institution.

3. Because of reasons discussed, it cannot be concluded that the apparent increase in incidence is significant.

4. The average duration of life after onset of symptoms was 3.2 years in 87 patients with chronic myelogenous leukemia and 3.6 years in 49 patients with chronic lymphogenous leukemia. About 80% survived for 1 year, 40% for 3 years, 20% for 5 years, and 4% for 10 years or more. Autopsies were performed on only 60% of this series.

5. In this series of 87 patients with chronic myelogenous leukemia, the duration of life was shorter in the individuals having marked anemia, relatively low leukocyte counts, or evidence of bleeding before treatment was given than in those without these features. If more than one of these findings were present, the probability of an early fatal outcome was greater than if only one was present.

6. The patients with chronic lymphogenous leukemia having marked anemia had a shorter course than those with little or no anemia. The duration of life was slightly longer in individuals having relatively low leukocyte counts than in those with higher counts.

7. The duration of life after the onset of symptoms in 9 patients with chronic lymphogenous leukemia possessing specific skin lesions did not differ from those without specific skin lesions.

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FAILURE OF ELECTROMAGNETICALLY INDUCED HEAT TO INCREASE RENAL EFFICIENCY.

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DIATHERMY treatment over the kidneys has been shown¹¹ to produce no significant change in renal function as measured by urea clearance or in arterial blood pressure. Heating of internal organs by means of electromagnetic induction ("inductotherm") is believed to produce much higher temperatures in them.^{3,4,9} By this method greater heat is generated in the more conductive, that is, the more vascular tissues, and less in such tissues as skin, fat and bone.

Application of heat to an organ is generally thought to increase the flow of blood through it. It was, therefore, reasonable to believe that inductotherm treatment of the kidneys might increase the blood flow to them and that this might be demonstrated by means of urea and creatinine clearances.^{8,12} Although it has been shown that these two clearances generally parallel one another,^{1,2,5,7,13} it was possible that treatment might affect the two tests in a different manner indicating change in the normal relationship of glomerular and tubular activity. For this reason both tests were made.

TABLE I.—ANALYSIS OF DATA.

Case No.	Date.	Hour.	Urine volume, cc./min.	Blood urea nitrogen, mg./100 cc.	Urea clearance, % of normal.	Creatinine clearance, % of normal.	Blood pressure.	Temp., ° F.	Diagnosis.
1	1937. 12/6	1st	6.68	11.5	44.9	146/90	...	Acute nephritis
		*2d	1.35	11.5	32.7†	136/76	100.2	
		3d	4.8	11.5	40.2	138/82	99.8	
	12/7						144/90	99.6	
		1st	9.5	10.5	52.1	136/80	98.4	
		*2d	5.29	9.3	47.2	128/72	99.4	
		3d	4.91	10.5	40.6	124/76	99.4	
							134/88	99.0	
	12/20	1st	3.38	14.2	56.8	52.6	104/62	98.6	
		*2d	6.42	12.7	59.6	51.2	106/60	99.0	
		3d	7.66	13.0	54.3	52.6	106/68	98.6	
		4th	8.04	13.0	52.3	48.2	98.6	
		5th	5.66	12.3	45.6	41.2	106/68	98.6	
	12/30	1st	3.72	11.8	53.5	58.8	112/80	98.6	
		†2d and							
		3d	3.35	11.8	44.4	46.5	120/38	101.2	
		*4th	0.333	11.8	26.6†	20.7	112/50	103.4	
		5th and							
2	12/17	6th	2.50	11.8	21.7	23.1	120/76	101.0	Acute nephritis
		7th	4.34	10.9	28.2	32.5	110/54	99.2	
		1st	3.56	15.9	68.0	98/54	98.4	
		*2d	6.03	15.7	84.1	88/20	98.4	
		3d	5.95	15.0	70.4	108/52	98.4	
		4th	6.82	15.9	73.5	100/68	98.2	
		5th	7.0	15.0	78.2	98.8	
		1st	1.0	90.5	10.6†	176/110	100.6	
		*2d	1.05	94.1	11.4†	170/106	101.6	
		3d	1.23	95.6	11.3†	174/108	100.4	
3	12/8	4th	0.86	93.5	9.5†	188/120	100.4	Chronic nephritis
		1st	0.40	110.0	6.0†	5.7	190/96	102.4	
		*2d	0.47	116.0	6.4†	5.3	194/94	104.4	
		3d	0.38	106.0	5.1†	6.1	196/94	104.2	
		4th	0.5	113.0	5.8†	8.0	103.0	
	12/21	5th	0.31	109.5	5.3†	5.2	102.6	Chronic nephritis
		1st	1.81	101.0	8.1†	6.5	174/94	98.6	
		*2d	1.62	100.2	9.2†	6.9	168/82	99.0	
		3d	1.83	91.8	9.4†	8.1	168/90	97.6	
		4th	1.50	94.0	8.8†	6.5	98.0	
4	12/23	5th	1.96	96.0	10.0†	8.4	98.0	Chronic nephritis
		1st	2.22	65.6	12.4	14.1	176/100	98.4	
		*2d	2.44	67.8	12.2	16.5	182/86	98.6	
		3d	2.70	60.7	13.4	13.8	184/96	98.4	
		4th	2.20	66.4	10.5	12.5	185/94	98.6	
	12/28	5th	2.55	65.0	14.7	15.9	98.4	Hypertension
		1st	1.46	9.1	56.6†	65.5	174/120	98.4	
		*2d	5.04	9.5	55.6	54.6	168/90	98.6	
		3d	3.80	8.6	33.4	36.1	168/120	98.8	
		4th	7.92	8.1	66.9	86.6	162/114	98.8	
5	12/16	5th	6.57	8.1	64.1	73.0	180/122	98.4	Hypertension
		1st	9.15	10.4	64.5	63.1	182/114	98.4	
		†2d and							
		3d	4.02	9.4	40.6	43.9	182/112	101.0	
		*4th	0.63	10.9	23.8†	28.8†	138/84	103.4	
	12/10	5th	1.05	11.3	39.0†	60.0†	164/110	102.6	Hypertension
		6th	2.57	10.9	46.7	68.8	158/100	100.8	
		7th	1.83	10.6	28.3†	46.6†	156/110	98.6	
		1st	5.34	10.0	79.1	58.8	158/112	97.8	
		*2d	7.53	9.5	58.5	52.2	160/112	98.8	
6	12/15	3d	5.2	9.5	74.1	68.0	180/130	98.2	Hypertension
		4th	6.0	9.1	47.2	49.7	176/124	97.8	
		5th	9.5	8.6	74.6	66.4	98.0	
		1st	3.46	14.5	84.6	116.0	158/90	98.2	
		*2d	6.26	14.1	79.6	92.1	146/74	99.2	
	12/29	3d	7.38	13.3	112.0	128.0	170/88	98.6	Pernicious anemia with hypertension
		4th	4.46	13.3	78.9	103.0	164/94	98.0	
		5th	7.31	12.6	75.3	99.4	176/90	97.8	
		1st	1.83	9.0	96.5†	105.0†	208/110	98.6	
		*2d	1.34	9.0	95.6†	99.1†	176/100	99.4	
7	12/22	3d	2.07	9.4	90.0	98.8	172/102	98.6	Hypertension
		4th	6.04	9.9	101.5	116.6	174/100	98.6	
		5th	4.30	9.7	93.0	97.6	98.4	
		1st	7.46	11.8	66.0	64.1	192/102	98.6	
		*2d	4.43	11.3	61.1	71.4	186/108	100.4	
8	12/9	3d	5.26	10.6	59.1	58.5	190/104	99.6	Hypertension
		4th	10.85	10.1	80.3	81.8	212/114	99.6	
		5th	5.37	10.1	61.4	60.6	192/104	99.0	
		1st	6.0	16.2	115.0	105/66	98.4	
		*2d	4.58	15.7	81.6	100/60	99.0	
9	12/9	3d	1.83	15.0	76.1†	104/64	98.8	Rheumatic fever (acute)
		4th	8.46	14.1	111.2	98.2	
		5th	7.22	13.8	110.2	116/70	99.2	

* Inductotherm. † Standard clearance. ‡ Patient wrapped in blankets and inductotherm applied.

Methods. Urea clearances were ascertained by the method of Möller, McIntosh and Van Slyke¹⁰ and creatinine clearance by a modification of the method of Hanzal and Hayman.⁶ Following a control period during which clearances were determined, a large disk electrode of the inductotherm was applied over the region of the kidneys with the patient lying on his side. The intensity of the inductotherm was set at maximum and the treatment lasted 1 hour.

No attempt was made in most of the experiments to retain heat in the patient's body. Two patients (Cases 1 and 5) were wrapped in blankets and covered with a rubber sheet during application of the inductotherm to determine the effect of heat retention by the body on the kidneys.

Ten patients were studied, 2 with acute nephritis, 2 with chronic nephritis, 5 with essential hypertension, and 1 with acute rheumatic fever.

Results. When no precaution was taken to prevent dissipation of heat from the rest of the body the rectal temperature rose from 1 to $1\frac{1}{2}^{\circ}$, except in 1 (Case 3) where fever was already present. When this loss of heat was prevented by blankets the temperature rose to levels of 103° (oral).

During the period of heat treatment or in the periods following it, a moderate decrease in urea clearance occurred in 11 of 16 experiments (Table 1). The most marked decreases were observed when loss of body heat was prevented by means of blankets (Cases 1 and 5). When the renal efficiency was low, as in the 2 patients (Cases 3 and 4) suffering from chronic nephritis, no change in urea clearance was found. This is in agreement with many observations which indicate that the flexibility of response is lost when renal function is seriously impaired by chronic nephritis.

Creatinine clearances usually paralleled the urea clearances. Blood urea was unchanged as the result of heat treatment and urine volume varied irregularly. One patient (Case 3) who had marked edema showed no diuretic response after heat was applied.

It was hoped that heating the kidneys might cause relaxation of hypertonic arterioles, if such existed, in the kidneys of patients with early essential hypertension. If better perfusion of the kidneys with blood occurred, it was possible that arterial blood pressure might fall. Our results show, however, that neither was increased perfusion evident from the clearances nor was there more than slight fall in diastolic blood pressure.

The results of the clearances suggest that, even though heat is induced within the kidneys, dissipation to other parts of the body by the blood causes sufficient somatic vascular dilatation to decrease rather than increase the flow of blood to the kidneys.

Summary. Application of heat produced by electromagnetic induction ("inductotherm") to the region of the kidneys was attempted in patients suffering from acute and chronic nephritis, early essential hypertension and acute rheumatic fever. A slight decrease in renal efficiency as measured by urea and creatinine clearances was observed as a result in this experiment. As these clearances are a rough measure of renal blood flow, heat treatment

reduces rather than increases the flow of blood to the kidneys, possibly by producing vasodilatation in other parts of the body.

Diastolic blood pressure was moderately reduced while heat was being applied but quickly rose to its original level on discontinuing it.

We are indebted to Dr. George W. Stark of Syracuse, N. Y., for the suggestion that inductotherm heating might affect the efficiency of the kidneys, and to the General Electric Company for the loan of the inductothermy apparatus.

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CHEMOTHERAPY OF TYPES VII AND III PNEUMOCOCCAL INFECTIONS WITH SULPHANILAMIDE, 4,4'-DI-(ACETYL-AMINO)-DIPHENYLSULPHONE AND 4,4'-DIAMINO-BENZENESULPHONANILIDE.

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SINCE the almost simultaneous publications by Rosenthal¹³ and by Cooper, Gross and Mellon,⁶ both of the above groups ^{2,3,4a,b,8a,b,13b,14} as well as a number of other investigators^{7,10,11,15,16} have reported successful chemotherapeutic experiments with sulphanilamide or other sulphur-containing aromatic compounds in infections caused by pneumococci.

While it is recognized that this chemotherapeutic activity is fractional in degree when compared with that exhibited by these compounds against streptococcal or meningococcal infections, nevertheless their therapeutic action is undeniable and has been confirmed clinically.^{1,9,12} Up to the present time these drugs have

been found effective in mice, rats and rabbits and against Types I, II, III, and XIV pneumococci.*

In this paper we are reporting results obtained by the use of two relatively new compounds† in experimental infections caused by Types VII and III pneumococci. One of these compounds, 4,4'-diaminobenzenesulphonanilide, was first used by Whitby¹⁶ and later by Bauer and Rosenthal². The former reported this drug to be more effective than sulphanilamide against Type I pneumococcal infections of mice, whereas the latter authors found it "inferior to sulphanilamide against pneumococci." Fournau and coworkers⁷ first investigated the activity of 4,4'-di-(acetyl-amino)-diphenylsulphone and estimated that 1 mg. produced as much therapeutic effect as 10 mg. of sulphanilamide in pneumococcal infections. This compound was later investigated by Bauer and Rosenthal² who also found its antipneumococcal activity superior to that of sulphanilamide.

Method. Groups of 30 to 40 mice or rats were inoculated with suitable dilutions of 18-hour broth cultures and treated orally 3 to 5 hours later with 5 to 12.5% suspensions of the various drugs (Figs. 1 and 2). Since different subcultures of stock strains were used for the several dilutions, the magnitude of the inocula was more relative than absolute.

In light of previous reports of the therapeutic superiority of the sulphone, it was assayed against $2\frac{1}{2}$ times the quantity of sulphanilamide in Exp. 1 A; against 2 times the quantity in Exp. 1 B and 1 C; and against equal amounts in Exp. 1 D.

Results. *Type VII, Mice.* A. (Fig. 1): While 70% of the controls died, the sulphone-treated mice showed a 30% (3 out of 10) mortality rate; and those treated with sulphanilamide, 10% (1 out of 10).

B. (Fig. 1): With treatment continued for only 4 days, there were 7 deaths out of 10 mice treated with the sulphone and 4 deaths out of 10 mice treated with sulphanilamide, contrasted with the 90% death rate in the control group.

C. (Fig. 1): Of 11 mice treated daily for 9 days with sulphanilamide, 7 died; of 11 mice similarly treated with the sulphone, 5 died; and of 10 mice treated with the anilide only 4 died. The control group had a 91% fatality.

D. With the inoculum administered intraperitoneally all controls died in less than 48 hours. The group treated with sulphanilamide had 4 deaths out of 10; that treated with the sulphone, 7 out of 10; and the group treated with the anilide, 8 out of 10.

Type III, Mice and Rats. A. (Fig. 2): With a heavy infecting dose of over 100 M.L.D., poor therapeutic results were obtained.

* While this paper was in press L. E. H. Whitby (Lancet, 1, 1210, 1935) reported excellent results against Types I, II, III, V, VII, and VIII pneumococcal infections in mice with the sulphonamide compound 2-(p-aminobenzenesulphonamido) pyridine.

† Supplied through the courtesy of the Monsanto Chemical Company, St. Louis, Mo. The sulphanilamide was furnished by E. R. Squibb & Sons, New York City.

All controls died in less than 3 days. The treated groups showed the following fatality rates: the anilide group, 5 out of 10; the sulph-anilamide group, 7 out of 10; and the sulphone group, 10 out of 10.

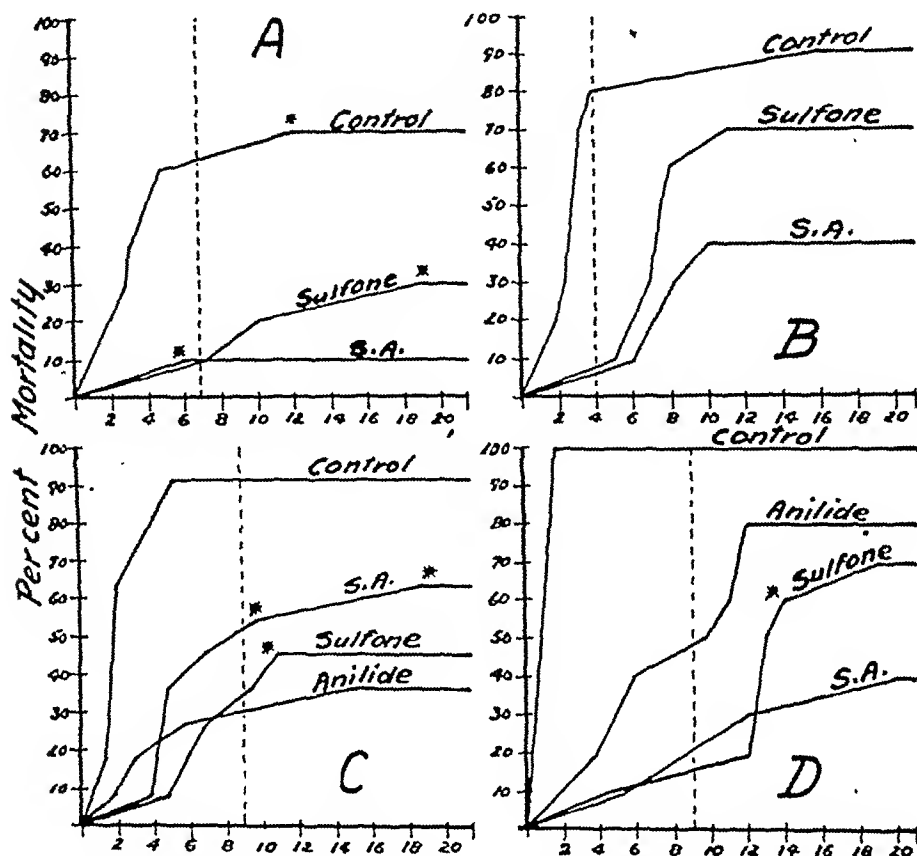


FIG. 1.—MORTALITY CURVES OF MICE INFECTED WITH TYPE VII PNEUMOCOCCUS (ENRICAST†).

Animals infected with diluted 18-hour broth cultures and treated orally each day. Treatment was begun 3 hours after infection and was terminated as indicated by the vertical broken line.

A. Infection: 0.5 cc. of a 10^{-8} dilution in broth, subcutaneously. Treatment: Controls: 10 mice, no treatment. Sulphanilamide: 10 mice, 25 mg. Sulphone: 10 mice, 10 mg. B. Infection: 0.5 cc. of a 10^{-6} dilution in broth, subcutaneously. Treatment: Controls: 10 mice, no treatment. Sulphanilamide: 10 mice, 10 mg. Sulphone: 10 mice, 5 mg. C. Infection: 0.5 cc. of a 10^{-4} dilution in broth, subcutaneously. Treatment: Controls: 11 mice, no treatment. Sulphanilamide: 11 mice, 10 mg. Sulphone: 11 mice, 5 mg. Anilide: 11 mice, 10 mg. D. Infection: 0.5 cc. of a 10^{-4} dilution in broth, intraperitoneally. Treatment: Controls: 10 mice, no treatment. Sulphanilamide: 10 mice, 25 mg. Sulphone: 10 mice, 25 mg. Anilide: 10 mice, 25 mg.

* Deaths not due to pneumococcus.

† Obtained from New York City Dept. of Health, 16th St. and East River.

B. (Fig. 2): Nine out of 10 control rats were dead in 6 days. None of the animals treated with sulphanilamide died. One out of 7 rats treated with the anilide, and 2 out of 9 rats treated with the sulphone died.

Throughout all experiments a definite increase in survival time of the fatalities among the treated animals over that of the controls was noted.

Discussion. Therapy with 4,4'-di-(acetylamino)-diphenylsulphone in infections of mice caused by pneumococci, Types VII and III was, in our experiments, not as effective as that with sulphanilamide. This is in apparent contradiction to the findings of Fourneau, *et al.*¹ and of Bauer and Rosenthal.² However, it appears probable that strain variations may account for the differences in the results obtained. As a matter of fact, Bauer and Rosenthal² encountered variation in the effectiveness of their drugs upon different types of pneumococci which they also attributed to strain differences.

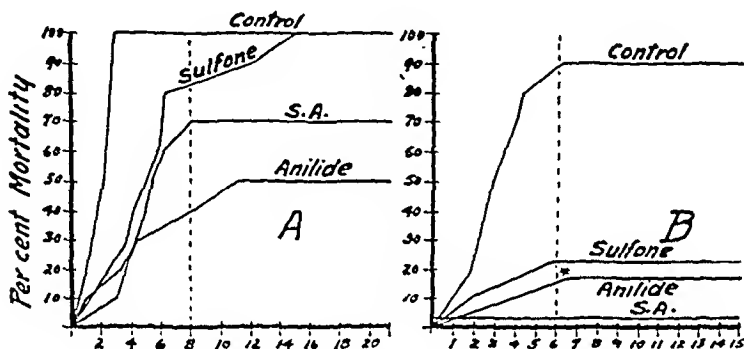


FIG. 2.—MORTALITY CURVES OF MICE AND RATS INFECTED WITH TYPE III PNEUMOCOCCUS (ALBANY).

Animals infected with diluted 18-hour broth cultures and treated orally each day. Treatment was begun $4\frac{1}{2}$ hours after infection and was terminated as indicated by the vertical broken line.

A. Infection: 0.5 cc. of a 10^{-6} dilution in broth, subcutaneously (more than 100 fatal doses). **Treatment:** Controls: 10 mice, no treatment. Sulphanilamide: 10 mice, 25 mg. Sulphone: 10 mice, 25 mg. **B. Infection:** 0.13 cc. of a mucin suspension of an 18-hour broth culture, diluted 10^{-2} , intratracheally. **Treatment:** Controls: 10 rats, no treatment. Sulphanilamide: 10 rats, 125 mg. Sulphone: 9 rats, 125 mg. Anilide: 8 rats, 125 mg.

In experimental pneumococcal pneumonia of rats, the sulphone therapy, while not as good as that of sulphanilamide, was nevertheless of considerable value. A consideration of the relative lack of toxicity^{2,5} of this drug, together with the previous favorable reports^{2,7} and the above rat experiment would make it appear that this compound is worthy of clinical trial, were it not for the fact that the results in our mouse experiments were distinctly less favorable than those reported with other pneumococcal strains.^{2,7} Our more recent and as yet unpublished results of sulphone therapy in Type II pneumococcal meningitis of rats were distinctly inferior to those obtained with sulphanilamide.

It has been our observation that intraperitoneal pneumococcal infections of mice constitute an extremely severe test of chemo-

therapeutic efficacy of a drug, that subcutaneous pneumococcal infections of mice give the drugs a better opportunity to manifest any possible chemotherapeutic activity,⁶ and that experimental pneumococcal pneumonia of rats is probably the best method^{4a,b, 8a,b} to date by which to measure antipneumococcal chemotherapeutic action.

Our search for cultures of high rat virulence has revealed a number of pneumococcal strains which, although lethal to mice in culture dilutions of 10^{-8} , are almost completely avirulent for rats. The "Enricas" Type VII strain reported above is a good illustration of this phenomenon.

Therapeutic results with 4,4'-diaminobenzenesulphonanilide were at times better than those obtained with sulphanilamide; however, its toxicity⁵ would seem to preclude any extensive clinical use.

Summary. 1. 4,4'-di-(acetyl-amino)-diphenylsulphone has been found less effective than sulphanilamide against pneumococcal infections in mice caused by a Type VII strain and a Type III strain, as well as in pneumococcal pneumonia in rats caused by this Type III strain.

2. The results reported, although at variance with those of other investigators, probably find explanation in differences of strain susceptibility to chemotherapy.

3. 4,4'-diaminobenzenesulphonanilide, although at times more effective than sulphanilamide against the particular pneumococcus strains tested, appears too toxic to warrant clinical trial.

4. To the infections caused by Types I, II, III, and XIV pneumococci which have previously been found susceptible to therapy by certain sulphonamide and sulphone compounds may be added those caused by the Type VII pneumococcus.

5. These experiments verify previous chemotherapeutic results in pneumococcal infections, namely, that little or no protection in mice may be demonstrated against more than 100 fatal doses, whereas good protection has been repeatedly reported against 10 fatal doses.

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STUDIES ON LIVER FUNCTION IN PNEUMOCOCCUS PNEUMONIA.*

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THE investigation herein reported attempts to determine the functional changes that occur in the liver during the course of pneumococcus lobar pneumonia. The recent literature on liver function has dealt in the main either with those disease processes of the liver and bile passages which are amenable to surgical treatment, or with chronic progressive changes attended by permanent damage. There have been some efforts made to determine the functional disturbances in acute infections; these, however, have in general embodied the use of single tests.^{5,7,14,18} The dangers of measuring liver function based on the ability of the organ to perform only one of its many functions, are well known. It therefore occurred to us that more accurate information might be obtained if an attempt was made to measure simultaneously more than one of the metabolic functions of the organ during the course of an acute infection. Accordingly, a series of patients suffering from lobar pneumonia were chosen for a study in which several tests were done concurrently in individual patients at varying stages of their illness. It was hoped in this way to accumulate sufficient data which, when analyzed in the light of the subsequent outcome of these cases, might provide us with further knowledge of the behavior of the liver in the course of this disease.

Material and Methods. The determinations from which an analysis was made resulted from a study of 80 cases of pneumococcus lobar pneumonia on the wards of the Fourth Medical Division of Bellevue Hospital during the season 1933-1934.† This group of cases offered an excellent opportunity for a study of this kind, in that the data on liver function was accumulated in the course of a controlled experiment to determine the therapeutic value of certain pneumococcus antisera.⁴ All the patients were under the immediate control of one of us, so that methods of therapy and

* Presented in part at the Sixteenth Annual Meeting of the American Society of Clinical Pathologists at Philadelphia, Pa., June 4, 1937.

† On the services of Dr. Charles Nammack, the late Dr. Harlow Brooks, Dr. Anna von Sholly and Dr. Harry Solomon, to whom we wish to express our great indebtedness.

dietary factors were identical in the group. All the observed cases showed evidence of definite lung consolidation, and the type of infecting pneumococcus was established in every instance.

At the outset, an attempt was made to choose methods of estimating liver function that were accurate, clinically convenient and that did not involve extensive technical procedures. With this in mind, three simple test methods were used; namely, the icterus index, the urobilinogen determination of the urine, and the levulose tolerance test; the first two being a measure of the pigment excretion, and the last one of the carbohydrate metabolism of the organ.

1. *Icterus Index.* Bernheim's¹ modification of the Meulengracht test was used. This appeared to us to be a good one to use, as it is generally agreed that the icterus index is as good a guide to bilirubinemia as the quantitative van den Bergh, provided that carotinemia can be excluded. It also has the advantage of being more convenient.

The samples of blood were taken for the most part at approximately the same time of day (9 to 11 A.M.). Following coagulation of the blood, the sera were promptly separated and read in a colorimeter. A glass standard was used and readings were made, using a standard source of artificial light. Sera that showed even slight hemolysis or turbidity were discarded. These observations were made from day to day during the course of the disease. In the analysis of the results, graphs were plotted showing the daily variation of the icterus index of the serum in each case. Values up to and including 7 were regarded as normal, a figure admittedly higher than that used by most workers. Values over 7 and up to 17 were regarded as indicating latent jaundice, while values over 17 were regarded as indicating clinical icterus. In determining the trend of the icterus index in the course of the disease (*e. g.*, whether the values were stationary, rising or falling) only variations of more than 4 units between successive determinations were thought worthy of graphic analysis.

2. *Urobilinogen.* The method used was that of Wallace and Diamond,¹⁶ a quantitative test based on the Ehrlich's aldehyde reaction. The dilutions of *freshly voided urine* ranged as follows: undiluted; 1:10; 1:20; 1:40; 1:80; 1:160; 1:320; and 1:640. Readings were made after 15 minutes so as to allow the full development of the color in the highest dilution. The urine samples were obtained from patients at the same time of day as the blood samples for icterus index (9 to 11 A.M.).

This test is thought to be extremely delicate in detecting early or slight disturbance in liver function. With impaired function, the liver cells fail to a greater or lesser extent in carrying out their task of removing urobilinogen from the blood and it is excreted in greater than usual amounts in the urine. Normally, the test should be negative with dilutions of urine greater than 1:20. Posi-

tive reaction with dilutions of 1:40 or more, were considered pathologic for the purpose of analysis.

3. *Levulose Tolerance.* Kimball is inclined to view levulose tolerance as a sensitive index of liver damage. In support of this latter claim may be cited the work of Folin and Berglund,⁶ Bodansky,² and Cathcart and Markowitz.³ Their results show that the metabolism of this sugar is handled almost entirely by the liver, where it is removed from the portal blood and converted into glycogen. During this process, no marked rise in the blood sugar occurs, as is seen when sugars like glucose and galactose are utilized by normal subjects. The work of Bodansky² clearly illustrates the difference in the metabolism of this sugar between normal animals and those in which liver damage is caused by such poisons as chloroform and phosphorus. He found after poisoning, a marked decrease in the levulose tolerance, which was comparable to the degree of liver damage noted at necropsy. From this, he concluded that this test gave reliable information in respect to the functional capacity of the liver in dogs.

In this present study, blood sugar curves were used as indices of levulose tolerance rather than determinations of urinary sugar excretion, because of the well-known fact that certain decomposition products of the sugar are of themselves non-fermentable reducing substances. Furthermore, blood sugar determinations obviate the introduction of the renal factor of permeability.

Kimball's⁹ modification of the levulose tolerance test was used: 50 gm. of the sugar is administered by mouth, and the fasting, 1-hour, and 2-hour blood sugar levels are determined. The chief criterion of impaired liver function is an elevation of 30 mg. % or more above fasting level in the first hour or of 15 mg. % or more above fasting level the second hour. The levels of blood sugar which continue elevated in the second hour are important, signifying as they do, the continuing inability of the liver to metabolize the sugar. A curve that rises in the second hour greater than the level of the first hour means serious hepatic insufficiency, provided that the first rise is sufficient to prove that absorption is satisfactory.

Experimental Data. 1. *Urobilinogen Test.* Five hundred and sixty tests were done on 80 patients, the number of tests varying in the individual case from 1 to 15. An analysis of these results based on the changes noted in relation to the progress of the disease and to the final outcome, was made.

Of these 80 cases studied, 50 recovered from their disease. From Table 1, it is seen that 32 cases (64%) showed abnormal urobilinogen values at some time or other of their disease. A further attempt was made to estimate graphically the individual trend of urobilinogen excretion in recovered cases which showed abnormal levels. It is found that 27 (85%) of these 32 cases shows a falling trend in the excretion of the pigment as the disease progressed from day to day.

Of the 30 fatal cases, abnormal values were obtained in 22 (73%). Furthermore, of this group there were 5 cases (16%) showing an excretion ranging from 1:160 to 1:640, a percentage twice as high as that seen in the recovered case.

TABLE 1.—LEVELS AND TREND OF UROBILINOGEN EXCRETION IN URINE.

	Moderately high pigment excretion 1:40 to 1:80.	Markedly high pigment excretion 1:160 to 1:640.	Cases showing falling trend in pigment excretion.
Recovered cases	28 (56%)	4 (8%)	27 (85%)
Fatal cases	17 (57%)	5 (16%)	7 (32%)

An analysis of the trend of the individual curve in this fatal group shows that only 7 of 22 cases (32%) show a falling trend in urobilinogen excretion. This is a striking difference when compared with the 85% of the recovered cases which show such a trend.

It is reasonable, therefore, to infer that, while single urobilinogen determinations have little prognostic significance, serial observations in the course of the disease show falling values in the recovered cases, with rising or persistently high values in the fatal cases.

2. *Icterus Index.* Four hundred and sixty-five observations on the icterus index were made in 78 cases, the number of tests varying in the individual case from 1 to 14.

Icterus indices were obtained in 49 of the 50 recovered cases. As shown in Table 2, 35 cases (71%) had values in the range of latent jaundice, the remaining 10 (21%) exhibiting clinical jaundice. There were sufficient serial observations in 40 of the 45 recovered cases to permit an analysis of the individual trend during the course of the disease. It was found that 34 of the 40 cases (86%) showed a falling trend in the icterus index as the disease progressed.

Observations on the icterus index were made in 29 fatal cases, 22 of these (76%) showing abnormal values. Of this fatal group, 16 cases (55%) showed values within the zone of latent jaundice, the remaining 6 (21%) exhibiting clinical jaundice. It was possible to analyze the trend in 18 of these 22 cases. Only 6 of these 18 (33%) (Table 2) showed a falling trend in the icterus index as the disease progressed. If a comparison between the fatal and recovered cases is made on the basis of a falling icterus index, it is seen that 33% of the former show this trend as compared to 86% of the latter.

TABLE 2.—DEGREES OF JAUNDICE AND TREND OF ICTERUS INDEX.

	Zone of latent jaundice readings 7 to 17.	Zone of clinical jaundice readings over 17.	Per cent of cases in which icterus index tends to fall in the course of the disease.
Recovered cases	35 (71%)	10 (21%)	34 (86%)
Fatal cases	16 (55%)	6 (21%)	6 (33%)

3. *Levulose Tolerance Test.* One hundred and sixty-four tests were done on 67 patients, the number of tests varying in the individual case from 1 to 5. In 46 cases, it was further possible to follow,

by means of serial determinations, the progressive changes in liver function. The analysis here has also been on the bases of recovered and fatal cases. The results are summarized in Table 3.

TABLE 3.—NATURE AND TREND OF LEVULOSE TOLERANCE.

	Abnormal response.	Cases showing im- proving tolerance.
Recovered cases	33 (77%)	25 (81%)
Fatal cases	24 (100%)	2 (29%)

In all, 43 recovered cases were studied. And in 33 of these (77%) the tolerance test showed abnormal values at one time or another in the course of the disease.

Moreover, it was possible to obtain serial observations in 31 of these 33 abnormal cases. An analysis of the trends shows that in 25 of these 31 cases (81%) the levulose tolerance tends to return to normal limits during the period of observation (3 weeks). It is significant to note that none of the recovered cases showed decreasing levulose tolerance in the progress of their disease. In other words, there was never any tendency for decreasing levulose tolerance in the face of clinical improvement.

There were 24 fatal cases studied, in only 7 of which was it possible to follow by serial observations the trend of levulose tolerance. The reason for the small number of fatal cases studied serially was due to the fact that many of these cases died before this could be accomplished, some indeed being moribund on admission. In all 24 cases (100%), at least one levulose tolerance test was abnormal.

In the 7 cases where it was possible to obtain serial observations, in only 2 (29%) did the levulose tolerance tend to improve, in contrast to 81% for the recovered cases.

Variations in the Functional Tests During the Course of the Disease. It seemed of definite interest to determine the variations in the different functional tests as the disease progressed. If the daily average readings of the urobilinogen excretion in all of the recovered and fatal cases are obtained, and the results expressed in the form of a graph, certain essential facts are illustrated. Thus, from Fig. 1 there appears to be little difference in the urobilinogen excretion in the first week of the disease between the fatal and recovered cases. In the second week, there appears to be a somewhat greater divergence between the values of the two groups. This is particularly striking when the results of the third week are studied. It must be borne in mind, however, that the number of cases in this latter group are small, so that it is possible that the real difference is not as marked as the graph indicates.

Similarly, if a graph for the average daily icterus index is compiled (Fig. 2), it is seen that in the recovered cases, there is a regular descent in the curve which appears most steep in the first week. There appears also to be a plateau developing from the tenth to the

fifteenth day. In the third week, the values are, with one exception within normal limits. On the other hand, when one considers the

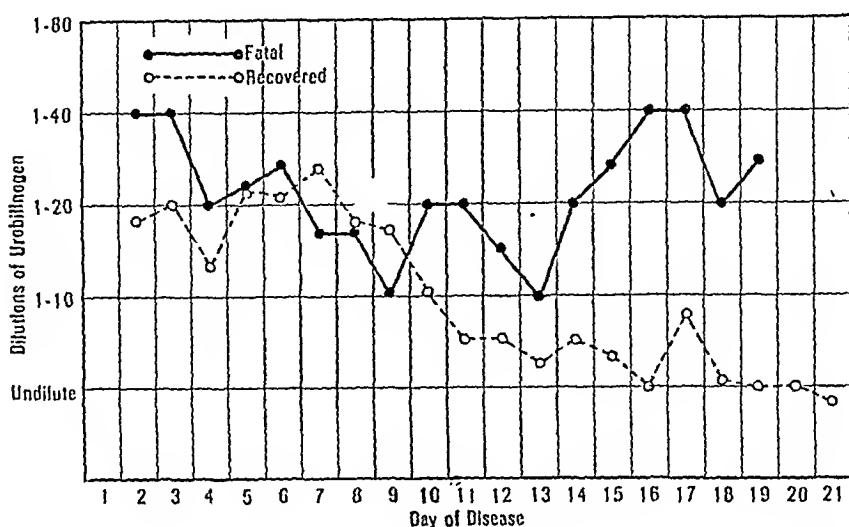


FIG. 1.—Composite daily values for urobilinogen excretion in the urine during first 3 weeks in recovered and fatal cases.

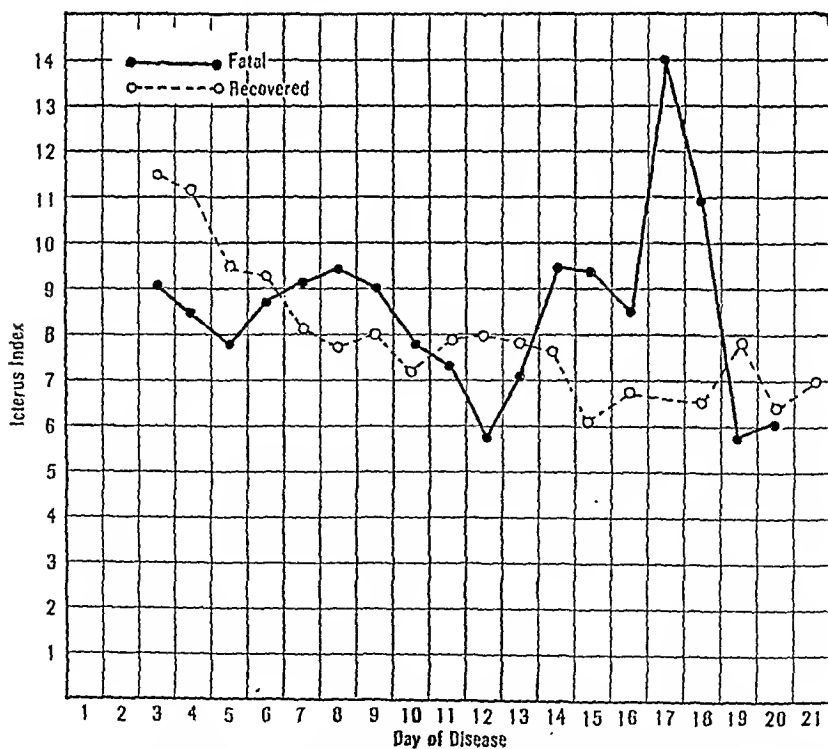


FIG. 2.—Composite values for icterus index in first 3 weeks in recovered and fatal cases.

fatal cases, one is first struck by the total irregularity of the contour of the graph. This is in some measure due to the smaller number of

observations in this group of cases. A closer analysis, however, shows that there is a tendency for the higher values to persist in the period from the sixth to the ninth day. It seems worth drawing attention to this because of the fact that the ultimate course of the disease appears to be influenced by the changes that occur in the patient in this period. That this observation in the fatal cases might be a reliable one is borne out by the fact that in this same period in the recovered cases, the average daily readings showed a constant fall. In the third week, it seems that most of the values are elevated, in contrast to the values observed in the recovered cases. If this be true, then daily observation of the icterus index in this disease might have definite prognostic importance.

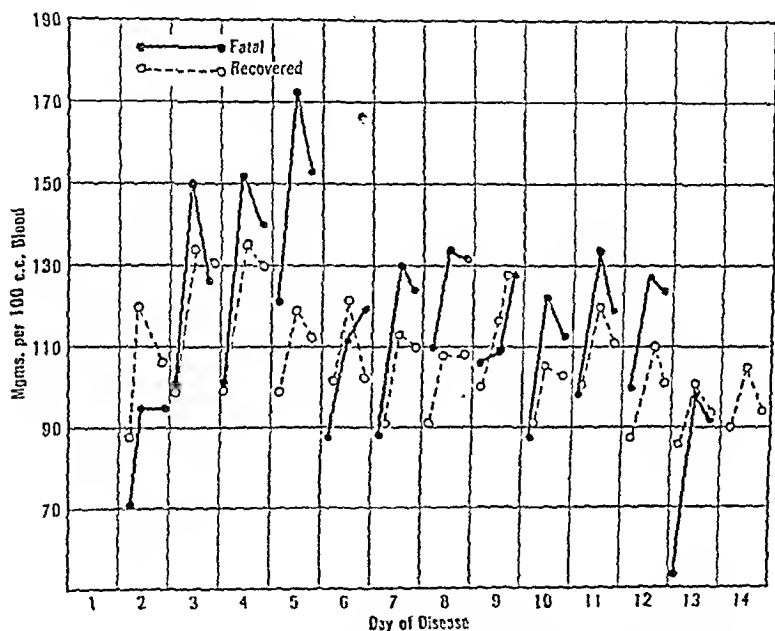


FIG. 3.—Composite curves of levulose tolerance, showing average fasting, 1-hour and 2-hour blood-sugar levels in first 2 weeks in recovered and fatal cases.

Similarly, if we analyze the levulose tolerance of these patients based on actual numerical values of their blood sugar levels, it becomes possible to compile therefrom a composite graph (Fig. 3). This illustrates a daily composite curve of the fasting, 1-hour and 2-hour blood sugar levels in both the fatal and recovered cases, during the first 2 weeks.

From this, it is seen that in the fatal cases, in almost every instance there is a well marked rise in the first hour readings above the fasting level, to be followed in most instances by either a slight fall, or even a continued rise. What is most noteworthy, however, is that the second hour level never falls within limits close to that of the fasting

level. On the other hand, analysis of the composite daily curves of the recovered cases shows levels in the first hour that are invariably lower than those seen in the fatal cases, with readings in the second hour which are not so far removed from the fasting level.

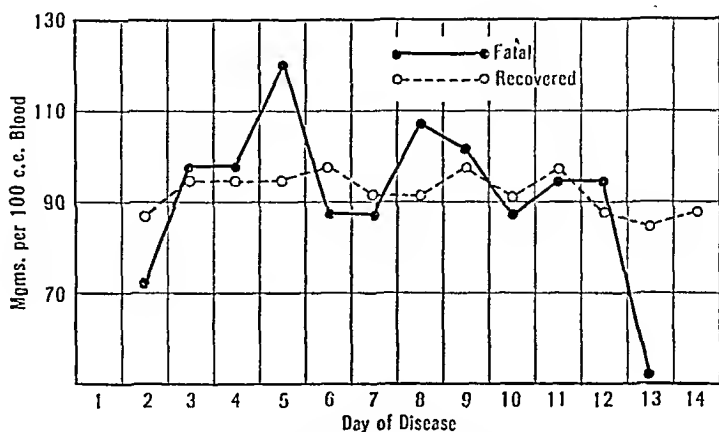


FIG. 4.—Composite fasting blood-sugar levels in recovered and fatal cases in first 2 weeks.

If one further compares the daily determination of the fasting levels in these two groups of cases (Fig. 4), it becomes at once apparent that there is a relatively narrow range of variation of the daily fasting levels in the recovered group for the first 2 weeks of the disease. Indeed, the range of fluctuation over this period is not greater than the actual technical variations that one might expect in performing this test. On the other hand, one observes from the figure the wide fluctuations of the fasting levels, throughout this same period in the fatal group, the outer limits ranging from 58 to 122 mg. per 100 cc. of blood. Aside, then, from the actual value of the levulose tolerance test, it would appear that a daily measure of the fasting blood sugar level might in itself supply us with an estimate of the function of the liver in this disease, as well as providing us with possible prognostic aid.

Relation of Liver Function to Infecting Types of Pneumococci. It seemed of interest to determine whether the functional tests demonstrated different degrees of liver damage in the different infecting types. An analysis was therefore made of the number of cases of each infecting type showing abnormal functional tests at one time or another in their disease.

TABLE 4.—ABNORMAL FUNCTIONAL TESTS IN RELATION TO INFECTING TYPES OF PNEUMOCOCCI.

	Urobilinogen.	Icterus index.	Levulose tolerance.
Type I	12 of 18 cases (67%)	13 of 16 cases (81%)	12 of 16 cases (75%)
Type II	15 of 18 cases (83%)	16 of 18 cases (89%)	16 of 17 cases (94%)
Type III	4 of 8 cases (50%)	5 of 8 cases (63%)	5 of 5 cases (100%)
Group IV	23 of 36 cases (64%)	29 of 36 cases (81%)	24 of 29 cases (83%)

From Table 4 it would appear that the Type II cases are attended by more severe liver damage than other types. This fact is in some measure borne out by the mortality rate in the series for this type, there being 17 deaths of 25 cases (68%), a rate that is considerably higher than that observed for the other types.

Discussion. For the purposes of clarity, it might be advantageous to summarize the information obtained from the individual tests as to liver dysfunction during this acute infection.

Urobilinogen. At the outset, it is necessary to note that our estimate of liver dysfunction by means of this test has been a conservative one. In this communication, the statistical results have been based on acceptance only of the values higher than 1:20 as abnormal, a dilution admittedly higher than that on which Wallace and Diamond base their conclusions when morning specimens are used. This normal value corresponds to that used by Rabinowitz.¹² Thus, on reviewing Table 1, the incidence of abnormal urobilinogen excretion is approximately equivalent in both recovered and fatal cases. Single abnormal values by themselves, therefore, would have no prognostic significance except, perhaps, in these cases in which the urobilinogen values are high. Thus, values ranging from 1:160 to 1:640 were found twice as frequently in the fatal group. However, it seems possible to obtain more prognostic help from the use of this test when serial observations are made from time to time during the disease. That a falling curve of urobilinogen values in a given case is of good prognostic omen, is evident from the fact that 85% of the recovered cases show such a trend in contrast to 32% of the fatal cases.

There seems to be scant reference in the literature as to the changes in urobilinogen excretion in pneumonia. Wilbur and Addis¹⁷ mention that the early appearance of large amounts of urobilin in the urine indicates a grave prognosis in pneumonia. Grönberg,⁷ in a small series of otherwise healthy young men with acute respiratory disease, notes an increased urobilinogen excretion during the febrile stage. Similarly, Harris's⁸ observation, in respect to pneumococcus lobar pneumonia, is in rather close agreement with our results, as he observed an abnormal increase in the urobilinogen excretion in all cases at some time during the acute febrile stage. These facts, in conjunction with our own findings, show clearly that the urobilinogen excretion is increased in pneumococcus pneumonia, and that it varies in direct relation to the severity of the disease. It also shows that unusually high abnormal values are more often associated with a fatal outcome than with recovery.

Icterus Index. A relatively larger number (92%) of the recovered cases show heightened icterus indices, in comparison to the fatal cases (76%) (Table 2). On the other hand, during the acute febrile stage, 86% of the recovered cases show a falling level, as compared to 33% in the fatal group.

The observations of other workers on estimation of the bile pigment in the blood in pneumonia are conflicting. Thus Harris,⁸ by means of serum bilirubin determinations, found bile-pigment levels to be unchanged in the large majority of his cases. Bernheim,¹ on the other hand, by means of the icterus index, found that all of her 39 cases of lobar pneumonia showed increased bile pigment in the blood. These apparent discrepancies may be attributed in large part to the lack of serial observations by these authors, as it was not uncommon in our series to find values that fluctuated above or below the accepted normal on different days of the disease. Despite the different results by these two workers, they nevertheless agree that increased bile pigment in the blood seems to offer a poor prognosis. This conclusion is open to question. In this connection, pertinent is Schiff's¹³ finding that in 826 cases of pneumonia 21 patients showed clinical jaundice, only 8 of whom died. He concluded from this that jaundice in pneumonia is not of specially serious prognostic omen. Similarly, Szarke's¹⁴ observations on 900 children led him to the same conclusions. In our own series of 80 cases, we were able to recognize jaundice in only 2, both of whom recovered. There were, however, 14 other cases with icterus indices in the zone of clinical jaundice, which for some reason were not clinically recognized as icteric by us. In this group of 16 cases, there were 6 deaths (37.5%), a figure which is not sufficiently higher than the usual mortality rate for pneumococcus pneumonia in this and previous seasons, to conclude that jaundice in itself is of bad prognostic omen.

Levulose Tolerance. Our results appear to have definite significance, both as to the absolute findings and as to the general indication of liver dysfunction that this test shows in common with the icterus index and urobilinogen determinations. Thus, if one considers abnormal values only, it is seen from Table 3 that 77% of the recovered cases and 100% of the fatal cases showed evidence of impaired levulose tolerance at some stage of the disease. This finding is further strengthened by noting the trend of successive tolerance tests in individual patients who recovered or died. Thus, 81% of the recovered cases showed a return to normal in the levulose tolerance, either in the febrile or convalescent stages of their disease. This is in sharp contrast to the findings in the fatal cases, in which only 29% showed any tendency to return to normal.

These findings are of definite interest, as they show clearly the behavior of the liver in respect to carbohydrate metabolism in this acute infectious disease. A review of the literature dealing with this phase of liver function has not rewarded us with information with which our results might be compared. Thus, while levulose tolerance has been studied in many diseases, such as surgical diseases of the hepato-biliary system, toxic hepatitis, cirrhosis, catarrhal jaundice, malaria and other conditions, we were unable to find any method-

ical study of the carbohydrate function of the liver in lobar pneumonia. Williams,¹⁸ in a study of levulose tolerance in malaria, however, secured single observations in 3 cases of lobar pneumonia and reported them as being normal. Van Creveld¹⁵ observed that in the course of scarlet fever there is little alteration in carbohydrate tolerance until the stage of convalescence is reached, which is in direct contrast to our findings in the course of pneumococcic pneumonia.

While our findings show the value of this functional test, it remains to be seen whether frequent or daily observations of the fasting blood sugar level in this disease might not in itself provide us with equally valuable prognostic information. This is suggested by Fig. 4 in which a composite graph of the fasting levels of the fatal cases show more marked daily fluctuation than that seen in the recovered cases. Whether this is true or not can only be substantiated by further detailed study.

These findings as to the carbohydrate metabolism in our group of cases would lend support to certain recently reported therapeutic attempts¹⁰ in which good clinical results were described, following the use of large doses of dextrose intravenously in lobar pneumonia. This is supported by the work of Opie and Alford¹¹ in which they found that following liver damage with chloroform, rats subsisting on a carbohydrate diet survived the intoxication, while similar animals on a meat or fat diet died.

In conclusion, it seems important to emphasize the fact that individual single tests of liver function for prognostic purposes have little or no real value. Furthermore, our results show that different test methods applied to liver function during this disease are not susceptible to too close a correlation, as it is possible to obtain a normal result with one test and an abnormal value with another test on the same day of the disease. It is evident, however, that serial tests by different methods do offer observations which when taken together give us a fairly close idea as to the severity of the disease in the individual case, providing us as well with knowledge that has some prognostic significance.

Summary. 1. Multiple methods embodying the study of pigment and carbohydrate metabolism have been utilized concurrently in a study of liver function in 80 cases of pneumococcus pneumonia.

2. The urobilinogen excretion was increased in the majority of both the fatal and recovered cases, and markedly high values of excretion are twice as frequent in the fatal group. When serial observations were made from day to day in the course of this disease, the level of pigment excretion in the urine tended to fall in the recovered cases, but to remain persistently high or to rise in the fatal group.

3. The icterus index was elevated in both fatal and recovered cases in the early stages of pneumococcus pneumonia. There was

a constant tendency to falling icterus index values in the cases that recovered and a tendency to remain high in the fatal cases.

4. There is decreased levulose tolerance in a high percentage of the recovered cases and in all of the fatal cases early in the disease. Serial observations in fatal cases show a progressive decrease in the ability to metabolize the sugar; whereas in the cases that recover, there is a progressive increase in levulose tolerance.

It is a further question whether daily determinations of fasting blood sugar levels do not provide definite information of similar significance as that afforded by levulose tolerance tests.

5. These observations stress the importance of serial determinations in any functional test in the course of the study of an acute infectious disease like pneumonia.

The authors desire to express their sincere appreciation to Dr. Herman B. Baruch, the founder of the Simon Baruch Foundation, for the interest and the funds supplied for this investigation and to Mr. Harold Twining for the technical assistance in this study.

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NOTE ON RAPID DESENSITIZATION IN A CASE OF HYPERSENSITIVENESS TO INSULIN.

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THE purpose of this brief communication is to report the treatment and control of the diabetes in a case of hypersensitiveness to insulin by a method which, though not new in principle, has not been widely used.

Case Report. A female, age 56 (Hosp. No. 2381/36), was admitted to the Montreal General Hospital on May 1, 1936, with cellulitis of the right foot, which followed an injury to a callus. The diabetes was first discovered in April, 1927, during treatment of an axillary abscess. At that time, the

disturbance of the carbohydrate metabolism was relatively mild; after incision of the abscess, the hyperglycemia and glycosuria were well controlled with small amounts of insulin and with the low-carbohydrate-high-fat diet then in use, namely 50 gm. carbohydrate, 150 gm. fat, and 50 gm. protein. The wound healed satisfactorily. There was then no urticaria nor other sign or symptom suggesting hypersensitiveness to insulin.

TABLE 1.—SHOWING METHOD OF DESENSITIZATION IN A CASE OF HYPERSENSITIVENESS TO INSULIN.

Time.	Insulin.		Reaction.	Blood sugar, %.	Remarks.
	Site.	Units.			
7.30 A.M.	I.D.	0.2	Wheal 4 sq. cm.	0.192	Fasting state Breakfast
7.50	I.D.	0.2	Wheal 3 sq. cm.		
8.10	I.D.	0.4	Wheal 4 sq. cm. with pseudopod		
8.15	I.D.	0.8	Wheal 6 sq. cm. with pseudopod		
8.30	S.C.	0.2	Very slight induration	...	I.D. wheals fading
8.50	S.C.	0.4	No induration		
9.05	S.C.	0.8	Slight induration		
9.20	S.C.	1.6	Moderate induration		
9.40	S.C.	1.6	Very slight induration	...	Lunch
10.00	S.C.	3.2	Slight induration		
10.20	S.C.	3.2	No induration		
10.45	S.C.	6.0	Slight induration		
11.20	S.C.	9.0	Very slight induration	...	Carbohydrate, 30 gm. orally.
12.00 NOON	S.C.	14.0	No induration		
12.30 P.M.	S.C.	20.0	No induration		
1.10	S.C.	40.0	Moderate induration		
2.40	I.D.	4.0	Wheal 4 sq. cm. with pseudopod	0.059	Dinner I.V. 5% glucose started.
2.45	S.C.	40.0	Slight induration		
4.00	I.D.	4.0	Wheal 3 sq. cm.		
4.25	I.D.	4.0	Wheal 3 sq. cm. with pseudopod		
4.30	I.V.	0.4	None	...	I.D. reaction of 6.15 P.M. subsiding.
6.15	I.V.	1.0	None		
6.45	I.V.	2.0	None		
7.00	I.V.	4.0	None		
7.10	I.V.	8.0	None	...	Sips of orange juice with sugar.
7.25	I.V.	12.0	None		
7.40	I.V.	16.0	None		
7.55	I.V.	20.0	None		
8.10	I.V.	30.0	None	...	Sips of orange juice with sugar.
8.25	I.V.	4.0	Slight wheal with rapid absorption		
8.50	I.D.	4.0	Wheal 4 sq. cm. with pseudopod		
9.00	I.D.	4.0	Wheal 4 sq. cm. with pseudopod		
9.25	I.V.	1600 cc	I.V. discont. Total 1600 cc	0.040	Carbohydrate, 15 gm. orally.
10.00	I.V.	15 gm. orally.	Carbohydrate, 15 gm. orally.		

I.D. = intracutaneous. S.C. = subcutaneous. I.V. = intravenous.

The course of the diabetes was uneventful until another attack of cellulitis of the foot, October 6, 1934. Again, in spite of the infection, the diabetes was controlled satisfactorily with insulin, but each injection was followed by an urticarial reaction at the site of injection. On the 11th day of treatment, the urticaria spread over the whole body, and resistance to insulin, namely, difficult control of hyperglycemia and glycosuria was noted for the first time. A history was obtained of annually recurrent attacks of hay fever for many years, but of freedom from such attacks since 1929.

Intracutaneous tests were made with 1 unit dosages (0.1 cc.) of beef, hog, sheep, and crystalline insulin. The reactions were all alike, namely, formation of a wheal and an area of erythema of approximately 4 cm. square at 30 minutes after the injection. The insulin was therefore discontinued and an attempt made to treat the diabetes by diet alone. It was then found that though the blood was persistently hyperglycemic, the wound healed completely, but at a very slow rate. She was discharged from the hospital on March 14, 1935. On May 1, 1936, she was again admitted with cellulitis of the foot and, though there was no acidosis, the diabetes was under poor

control and could not be treated satisfactorily with diet alone. The above mentioned intracutaneous test was, therefore, repeated with crystalline insulin and it was found that the patient was still allergic.

In view of the surgical condition and the poor control of the diabetes with diet alone, an attempt was made to test the value of rapid desensitization with Connaught Laboratories commercial insulin. The amount of insulin, the time and site of each injection, the reaction to each injection, the treatment in general and results of periodic blood sugar determinations are shown in the accompanying table. The total volume of each intracutaneous injection was the same, namely, 0.1 cc.

It will be noted that practically complete desensitization was accomplished within 15 hours. At the end of 24 hours the reactions to intracutaneous tests were entirely negative.

Following the above procedure, an attempt was made to control the diabetes with the high-carbohydrate-low-caloric diet, which consisted of 220 gm. carbohydrate, 40 gm. of fat and 100 gm. of protein. It was then found that the diabetes was well controlled with 20 units of insulin daily. Two weeks later the dosage was reduced to 10 units. She was discharged from the hospital and 2 months later an intracutaneous test with 3 units of insulin resulted in formation of a slight wheal which persisted for about 1 hour. That the desensitization was sufficiently complete, however, was shown by the absence of other reactions and the satisfactory control of the diabetes. In November, 1936, when she was readmitted in spite of the appendix, the blood sugar was only 0.14% in the fasting state; the pre-operative and postoperative management were uneventful in spite of greatly increased insulin dosage. The patient has since remained under satisfactory control without a return of the hypersensitive state, on a high-carbohydrate-low-caloric diet with small doses of insulin.

Discussion. The antigen-like reaction of insulin⁴ and the clinical features of insulin hypersensitiveness¹ have recently been reviewed. Different methods of treatment of the latter have been suggested. Slow desensitization with therapeutic doses is not only uncomfortable on account of the local and general reactions, but may be harmful. When the hypersensitiveness is also accompanied by resistance to the injected insulin, this method is of little value because of the necessity of immediate control of the diabetes. Rapid desensitization has been reported to a tolerance 3,¹ 5³ and 6.2 units.² In 2 of these cases the results were not permanent.^{1,3} The advantages of rapid desensitization with small initial doses followed by large doses have been dealt with previously with respect to other substances possessing antigen-like reactions.⁵ The case reported here is an example of the applicability of this method to cases of hypersensitiveness to insulin.

The author wishes to express his gratitude to Dr. I. M. Rabinowitch for aid in the preparation of this report, to Dr. L. H. McKim, attending surgeon, for permission to report the case, and to the patient, a registered nurse, for her coöperation.

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SEMEN ANALYSES OF TWO HUNDRED FERTILE MEN.

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THE criteria that have been set up for the evaluation of human semen specimens have for the most part been formulated upon standards derived from the study of semen of men with histories of disturbed fertility. It is our belief, however, that a semen analysis of a series of fertile humans might more logically offer a better basis for appraisal.

Accordingly, the present investigation was undertaken to collect information relative to the semen of fertile men.

Methods. Fresh specimens were obtained from 200 husbands of pregnant women who were in the first half of gestation. All cases herein reported terminated with full-term deliveries of normal healthy children.

Two institutions served as sources for the material. The New York University College of Medicine, Department of Obstetrics and Gynecology; and the New York Hospital, Cornell University Medical College, Department of Surgery (Urology), and the Department of Obstetrics. Hereafter, the former group will be designated as Group I, and the latter as Group II.

One hundred random cases were selected and followed in each institution. The constituents of each group represented the widely varied Caucasian racial types that are to be found in metropolitan New York. Group I cases were referred from Bellevue Hospital, Department of Hospitals, New York City, which draws largely from the indigent section of the population, while Group II cases were patients of a pay clinic. Although the same plan and technique were used in each institution, each set of observations was made by independent workers, and no comparisons or analyses were attempted until both series were completed. Practical methods of semen analysis were favored above elaborate and complicated ones, and throughout the investigation a clinical viewpoint was constantly maintained. No special instruments were used which are not available in any clinical laboratory or physician's office.

Seminal specimens were collected by the patients after an advised period of 72 hours of continence. To 33 cases in Group I, washed and dried condoms were supplied, together with written instructions directing that, immediately after intercourse, the semen be emptied into a sterile test-tube, fitted with a cork stopper. The remainder (167) were instructed to collect their seminal discharge at the time of coitus by withdrawing and ejaculating directly into a large-mouthed sterilized glass test-tube. No effort was made to regulate the temperature of the specimen while in transport. More than half of the specimens were first examined within 3 hours of the time of ejaculation.

The volume of the ejaculate was measured in each case, and variations from 0.6 to 9 cc. were obtained. The average volume for all cases was 3 cc., whereas the condom group measured only an average of 2.3 cc. This in part accounts for a general lowering of the average volume of Group I patients, as compared with Group II (Fig. 1).

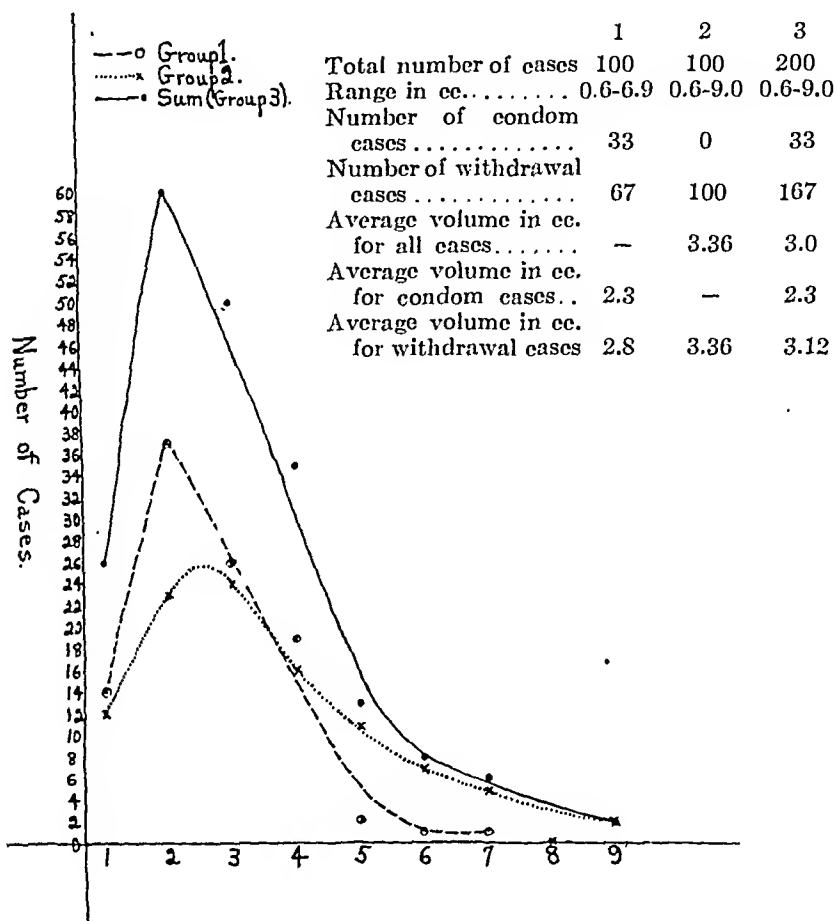


FIG. 1.—Semen volume in cubic centimeters.

The human ejaculate is a mixture of spermatozoa and the secretions from the epididymes, vasa, seminal vesicles, prostate, and the accessory glands of the urethra. The fluid content of the semen is said to carry nutritional elements for the spermatozoa. At the time of ejaculation, the specimen has a gelatinous consistency, but when it reaches the laboratory, self-liquefaction is complete and a uniform consistency is established. The spermatozoa comprise only a negligible portion of the bulk of the semen, as has been proven in vasectomized patients whose semen was repeatedly measured before operation.⁵ An initial postoperative decrease in volume is completely compensated for within 3 weeks after operation.

For the study of viscosity of fluid, various elaborate instruments are available. To conform with the practical applicability of this work, simpler methods were tried. Pipettes of various kinds were standardized with distilled water, and the rate of delivery was compared with that of semen. The factor of surface tension, however, is not eliminated in this method. A set of instruments of the Ostwald type, having different sized bores, could be adapted for use with semen. As one acquires experience in handling many specimens, it becomes relatively easy to judge normal viscosity and

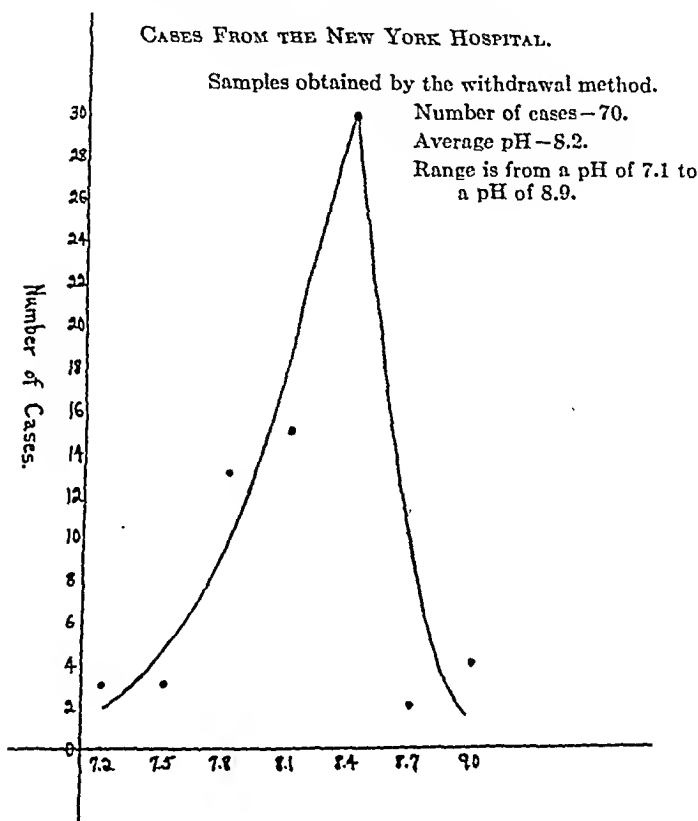


FIG. 2.—pH of the semen.

to evaluate turbidity without special instruments. Cary's³ simple method of testing the viscosity of cervical mucus was utilized for semen.

Messer and Almquest¹² have shown that the hydrogen-ion concentration of semen should be ascertained after precautions have been taken to prevent loss of carbon dioxide, due to exposure to air. The potentiometric method, using a quinhydrone electrode upon the semen collected under a layer of oil is too complicated for practical clinical application. Hydrogen-ion determinations were

made by the Pfaff colorimeter upon 68 specimens, and disclosed a range of 7.1 to 8.9. Messer and Almquest in 27 determinations found the mean pH to be 7.2, with individual variations over a range of 0.7 to 0.8 pH units. Baker¹ states that all sperm are killed at a pH of 5, and that they also exhibit poor motility between 6 and 6.9.

As can be seen from the accompanying charts, no correlation can be drawn between the hydrogen-ion concentration, as obtained by

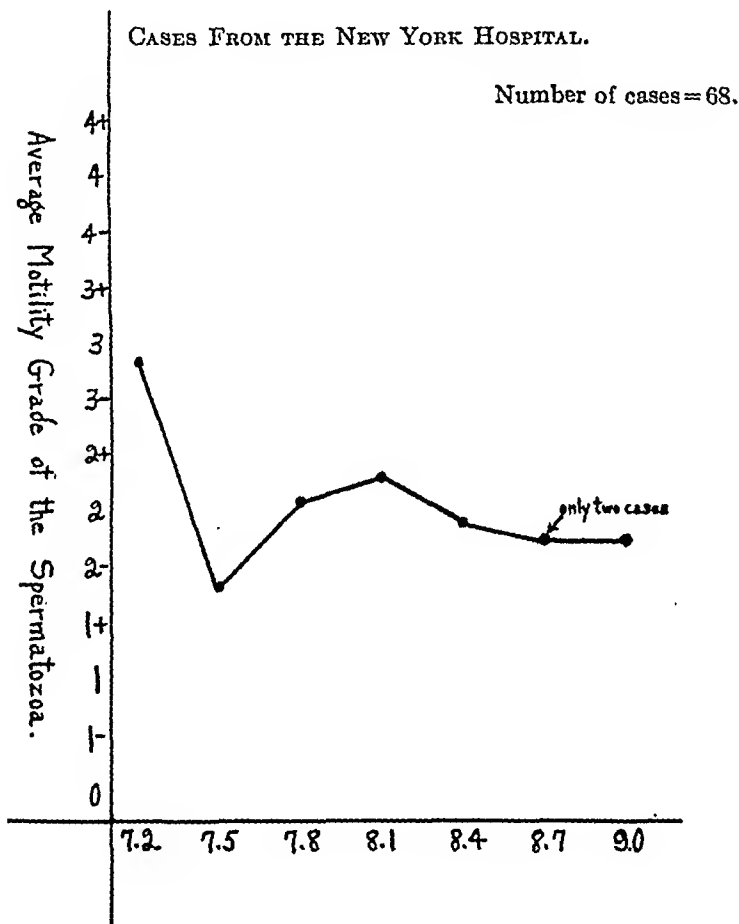


FIG. 3.—pH of the semen.

the colorimetric method, and the type and character of motility. Hence, when motility is satisfactory, it is unlikely that additional information is to be gained by a determination of the pH of seminal fluids (Figs. 2 and 3).

It is an accepted fact that living spermatozoa consume oxygen, give off carbon dioxide, and probably utilize sugar in their metabolism. Even approximate quantitative determination of sugar content of the semen requires time, special skill, and apparatus not generally possessed by the practising physician. The Benedict

modification of the Folin-Wu method for blood analysis was used to determine the sugar content of the semen.

Estimations were done in 64 specimens, using 0.5 cc. of semen as a sample for estimating the total reducible substance in the specimen. Ranges from 9 to 810 mg. per 100 cc. were obtained, the average being 306 mg. per 100 cc. of semen (Fig. 4).

A comparison between the grade of motility and the sugar content shows no clinical correlation. Accordingly, no apparent practical advantages are to be derived from this test (Fig. 5).

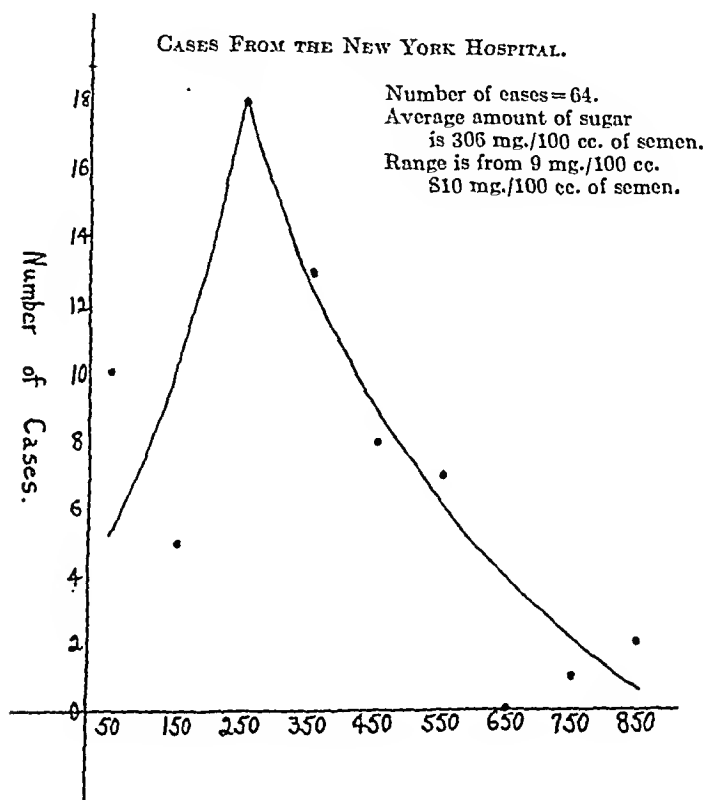


FIG. 4.—Amount of sugar in mg. per 100 cc. of semen.

The motility of the specimen should be evaluated on the basis of various factors; *i. e.*, type and aggressiveness of activity, percentage of inactive cells, and duration of motility. If the motility is poor, more than one specimen should be examined.

The method of collection is important in preserving good motility. A so-called semen sample produced by prostatic massage is mentioned only to be condemned, for it contains no more than the prostatic secretions with sometimes a few sluggish spermatozoa. Collection and delivery in rubber or skin condoms is the most com-

mon practice in clinical examinations. Because the former contains mica dust, sulphur, and benzine derivatives, and the skin condom must be wet before use, a definite damage is often done to the specimen by these contaminants. This can be demonstrated when the motility of the sperm so collected is compared with that of a withdrawal specimen from the same individual. Washed and dried condoms were supposed to have overcome this objection, but in 33 cases where these were used for collection, the motility was definitely inferior to the rest of the series.

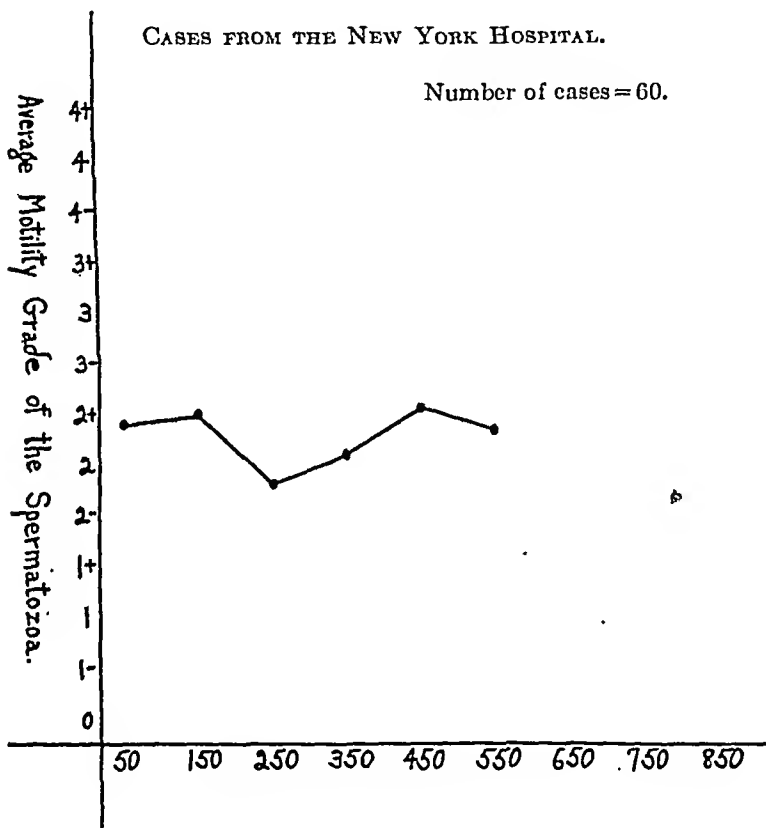


FIG. 5.—Amount of sugar in mg. per 100 cc. of semen.

Our experience bears out Belding's² contention that the optimal temperature for the preservation of motility is between 8 and 20° C. In good specimens, it is unusual to find appreciable change in the motility during the first 3 hours after ejaculation.

Active motility is considered to be a progressive, space-gaining movement across the microscopic field. Notations were made, using a slide and coverslip preparation, with a 4 mm. objective. In the majority of the cases, observations on the grade of motility were done within 3 hours. With few exceptions it was possible to make interval examinations every 3 hours during the day until the motility had stopped. Percentage of motility, as listed in Table A, means

the number of actively motile cells in relation to the total number of cells seen in each field.

% motility.	Grading.	% motility.	Grading.	% motility.	Grading.
0	0	35%	2	70%	3
5%	1-	40%	2	75%	3+
10%	1-	45%	2	80%	3+ or 4-
15%	1-	50%	2+	85%	4-
20%	1+ or 2-	55%	2+	90%	4
25%	2-	60%	2+ or 3-	95%	4+
30%	2-	65%	3-		

TABLE A.

At the end of 3 hours the average motility for 202 specimens was Grade 3-. During the course of these observations, Group I specimens were kept at room temperature and Group II at 20° C.

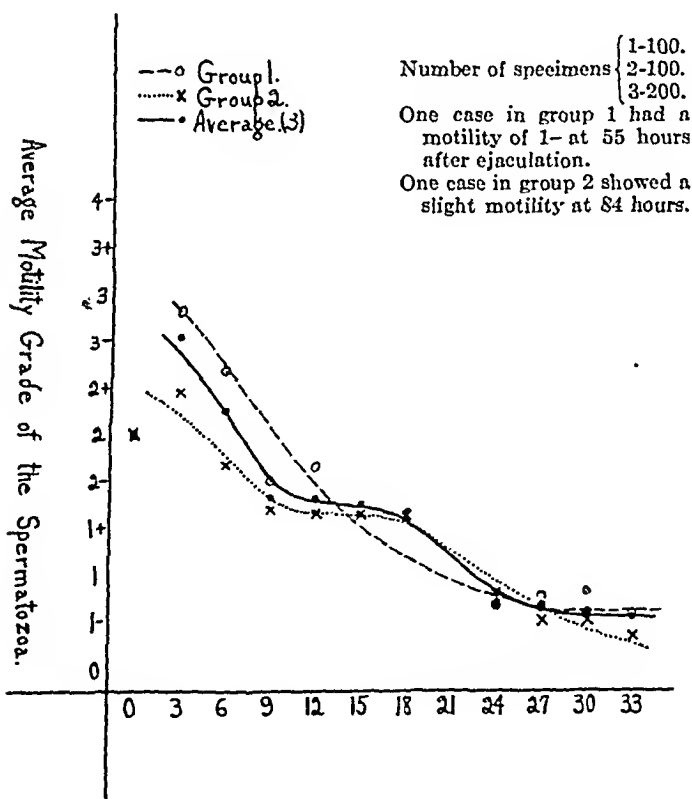


FIG. 6.—Time in hours after ejaculation of the semen.

There was no motility in 5 of 169 withdrawal specimens. One of these was first seen at the end of 30 hours. Another was collected and delivered in a perfume bottle, which may have caused contamination, thus accounting for this defect. Of the 33 condom

cases, 9 showed no initial motility. One specimen of Group I exhibited motility 55 hours after ejaculation, and in Group II, one showed slight motility at 84 hours.

Figure 6 shows the relationship of the grade of motility as compared to the age of the specimen. Prompt examinations of the semen are to be desired, but specimens presenting better grades of motility may be evaluated 3 to 9 hours after collection.

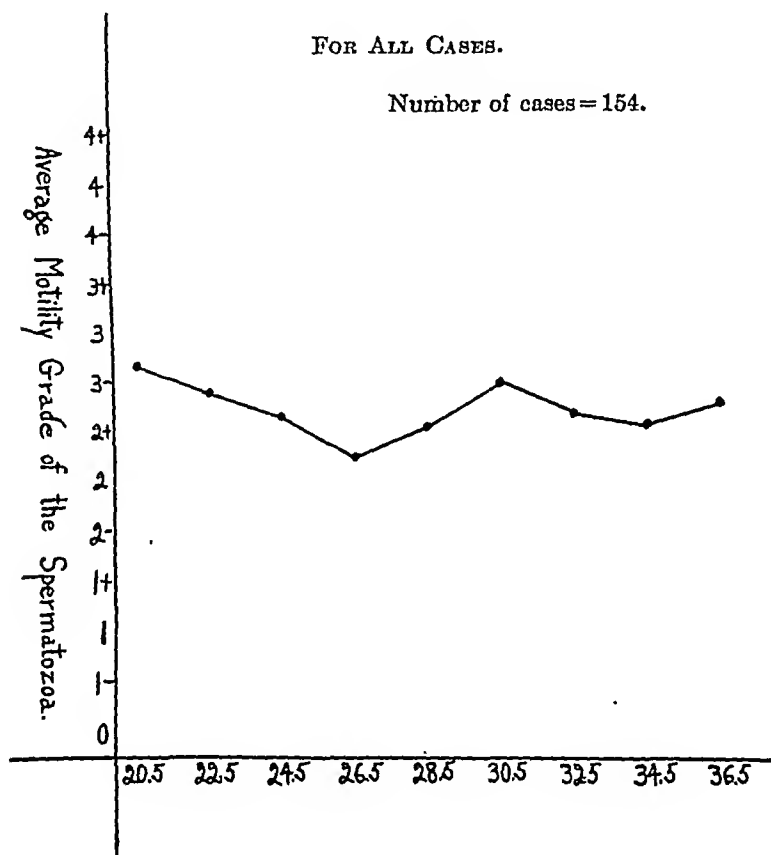


FIG. 7.—Age of men in years.

Figure 7 compares the type of motility with the age of the men. No profitable deductions can be drawn.

The number of spermatozoa found in 1 cc. is commonly used to designate the cell count. A determination of the number of sperm in the total ejaculate is obtained by multiplying the count per cc. by the volume of the entire ejaculate. The technique described by Macomber and Saunders,¹⁰ Vose,¹⁴ and Belding² was followed. More accurate counts are made within the first 3 hours after ejaculation, for after that period a certain amount of agglutination of the spermatozoa has occurred. Slight clumping of the cells occurs with ageing of the specimen, and errors are introduced which are not present in the fresh ejaculate. Each specimen was thoroughly

mixed by shaking before a sample was taken, and at least three separate counts were made. If numerous cells were present as observed through the high dry lens, a 1 to 20 dilution was used. If the number of spermatozoa was obviously reduced, a 1 to 10 dilution was preferred. All dilutions were made with standardized white blood cell pipettes, and a fluid consisting of a saturated solution of sodium bicarbonate and 1% phenol. A counting chamber with the Neubauer ruling was employed. The area studied was the red blood cell field, which occupies a space 1 by 1 sq. mm. If the cells found therein were few in number, all those within this

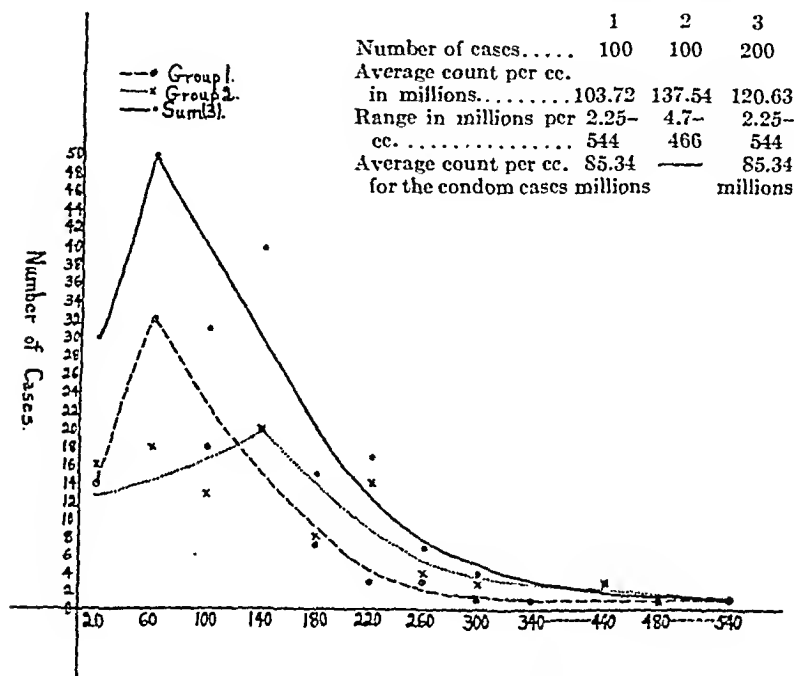


FIG. 8.—Spermatozoa count in millions per cc.

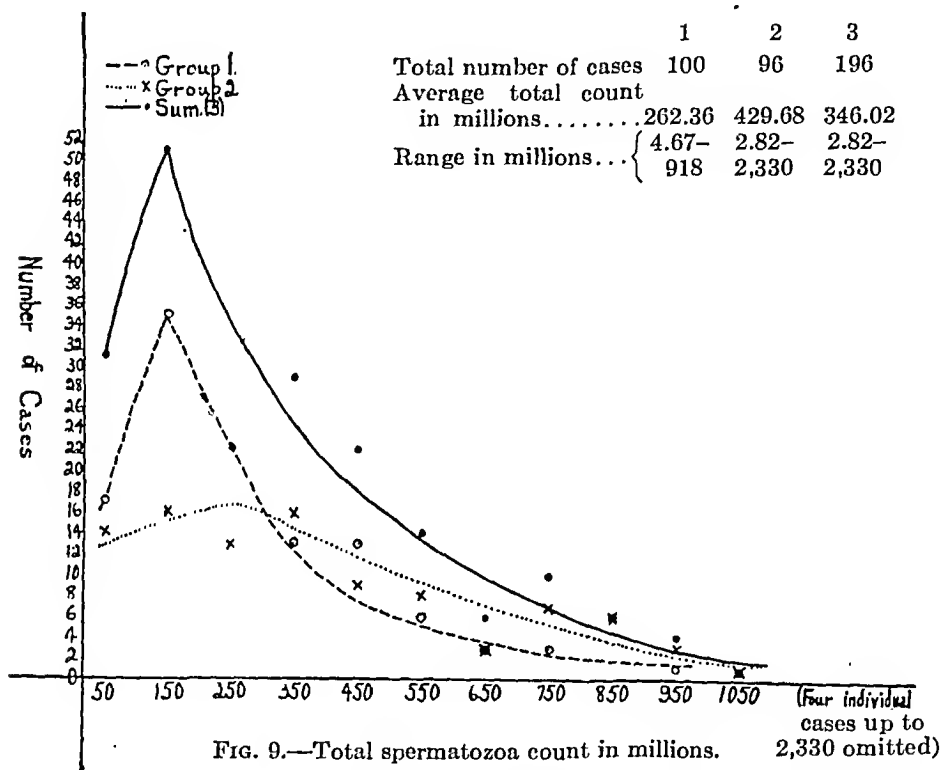
area were counted. If, however, many cells were found in the field, accurate results were obtained by counting 5 blocks of 16 squares, or one-fifth of the red blood cell field. By adding 6 ciphers to the latter figure, the number of sperm in 1 cc. was arrived at. It is recognized that a 10% variation in the final counts is not inconsistent with good technique.

Meaker¹¹ states in his text: "Most men who are highly fertile have counts over 100,000,000, and in our experience no pregnancy has occurred where the sperm count was below 60,000,000. Macomber and Saunders, in a series of 244 cases of fertile and sterile matings, have 4 cases where pregnancies have occurred with counts less than 60,000,000. It is assumed that both these investigators were quoting counts of sperm content per cc.

Belding² believes that the count per cc. may vary according to the activity of the prostate and seminal vesicles, and therefore considers the total count for the ejaculate to be more consistent and reliable.

Our results are tabulated in both cubic centimeters and total number of spermatozoa per ejaculate (Fig. 8).

The count per cc. varied from 2,250,000 to 544,000,000; the average being 120,630,000.



In the group of cases where condoms were used for collection, the counts were consistently lower, reaching the average of 85,340,000 per cc. This discrepancy might be partially explained by the presence of extraneous materials in the sheaths, which caused agglutination of the sperm, and prohibited uniform dilution.

In the accompanying tabulation, cases which showed a count below 60,000,000 per cc. were summarized.

(Count (per cc.).	Group I cases.	Group II cases.	Total cases.
Less than 20,000,000	9	1	10
Between 20,000,000 and 40,000,000	5	15	20
Between 40,000,000 and 60,000,000	14	8	22
	<u>28</u>	<u>24</u>	<u>52</u>

Thus it is seen that more than one-quarter of the cases studied had cell counts under 60,000,000 per cc. (Fig. 9).

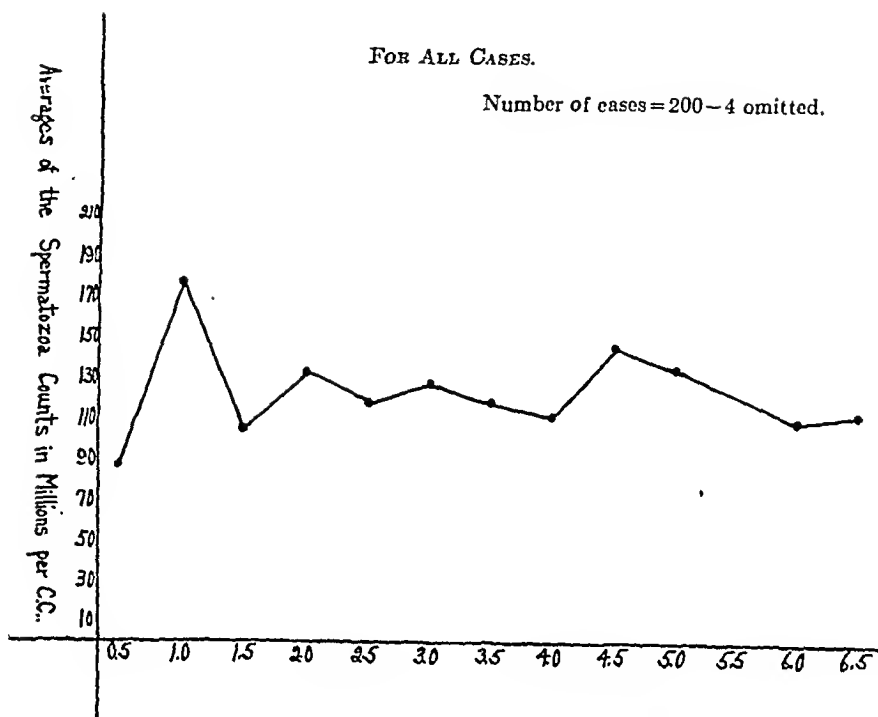


FIG. 10.—Semen volume in cubic centimeters.

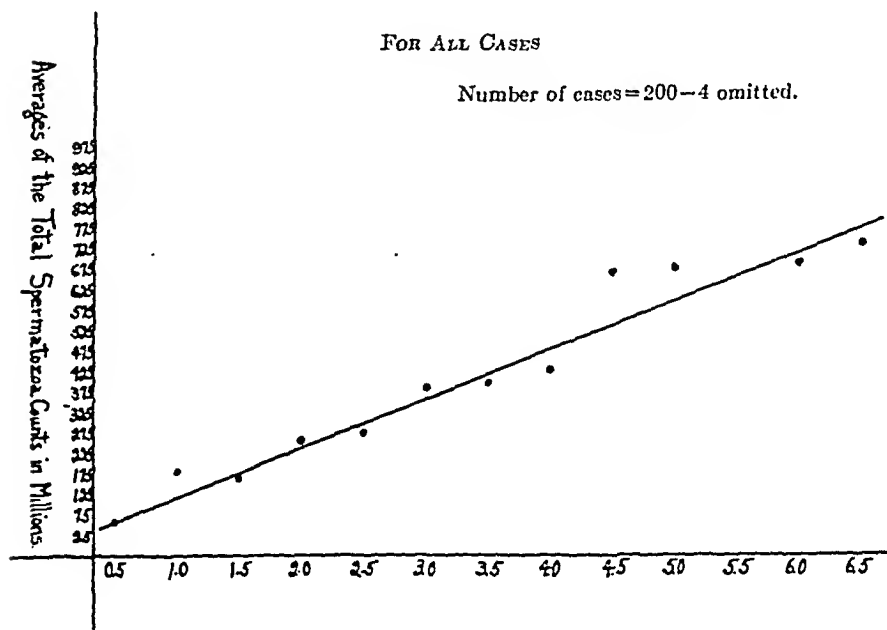


FIG. 11.—Semen volume in cubic centimeters.

The total number of spermatozoa in the ejaculates varied from 2,820,000 to as high as 2,330,000,000; the average being 346,020,000. Compiling the cases with low total counts, the following summary may be made.

Count (total).	Group I cases.	Group II cases.	Total cases.
Less than 50,000,000	6	5	11
Between 50,000,000 and 100,000,000	11	9	20
Between 100,000,000 and 150,000,000	23	8	31
	<hr/> 40	<hr/> 22	<hr/> 62

No relationship exists between the amount of ejaculate and the spermatozoa count per cc. (Fig. 10).

FOR ALL CASES.

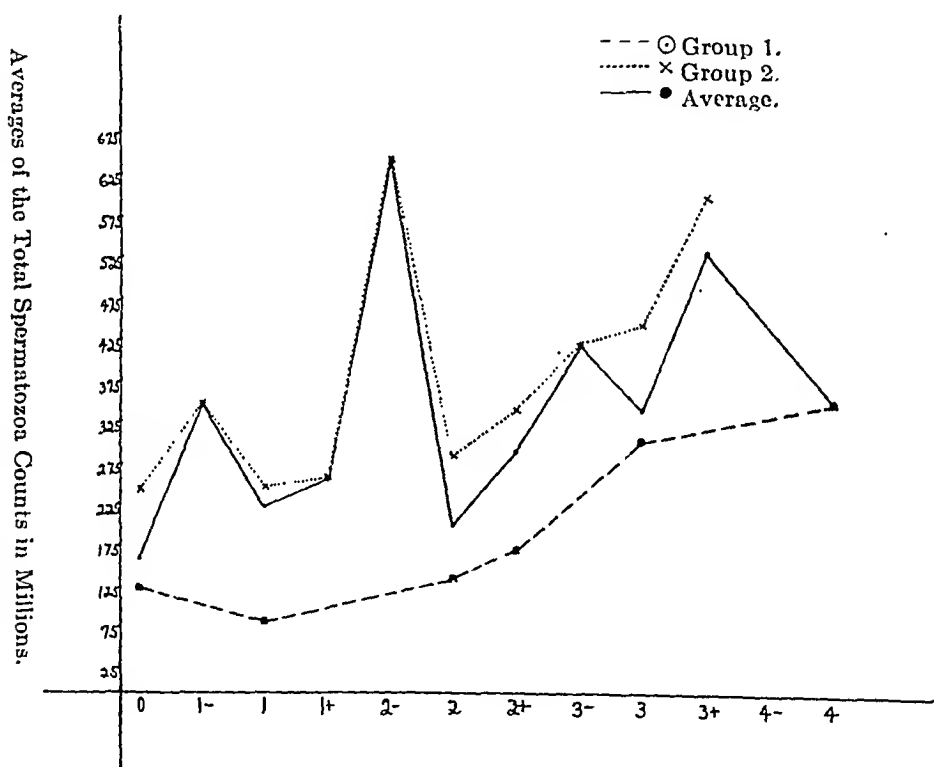


FIG. 12.—Motility grade of the spermatozoa.

Hence, it appears that a small volume does not necessarily indicate a concentration of the cellular elements, nor a large volume a higher dilution.

Figure 11 illustrates that in general the larger the volume, the higher the total cell count.

Specimens with higher cell content with few exceptions exhibit better grades of motility (Fig. 12).

Let us emphasize here that these relationships between volume and cell content, and between volume and motility, are based on a

population study and cannot be used as a standard for the individual.

Williams and Savage,¹⁵ in 1925, investigated the semen of bulls with "good" and "bad" breeding records. Detailed measurements were taken of the head of the sperm, and conclusions were drawn that the "morphology of the head of the sperm constitutes the greatest single source of information as to the fitness of cells for reproduction." Bulls with poor breeding records were found to have an average of 50.1% abnormal cells, while in animals with good breeding records, the abnormal sperm count did not exceed

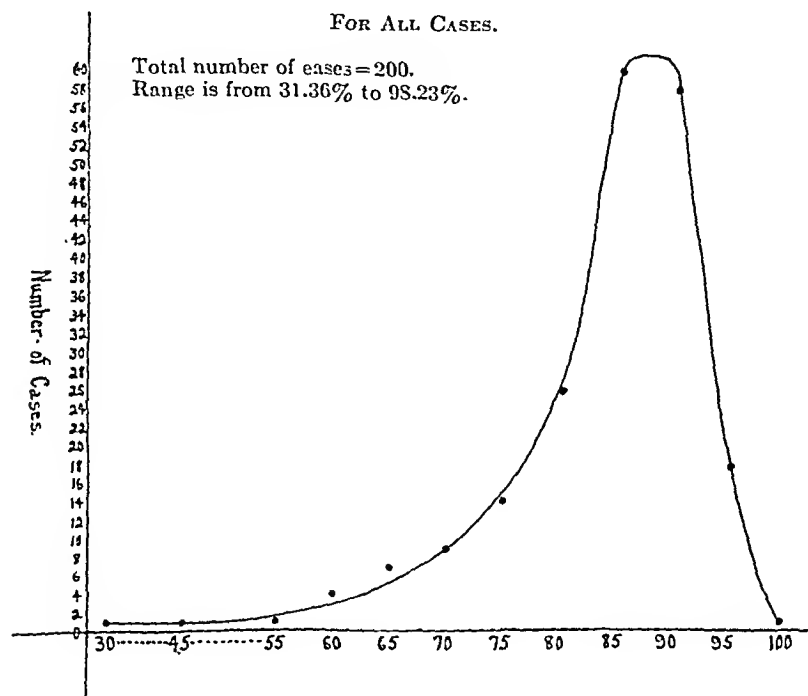
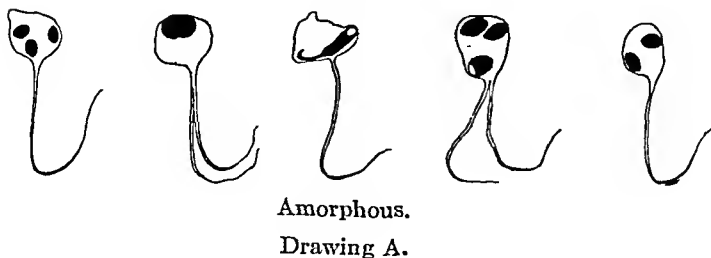
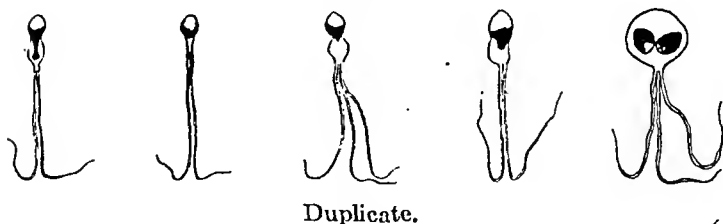
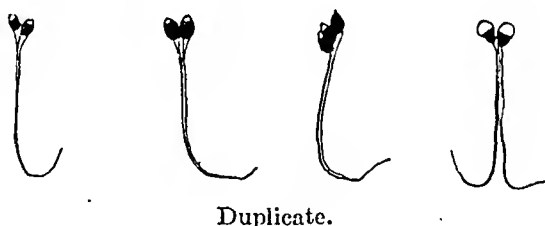
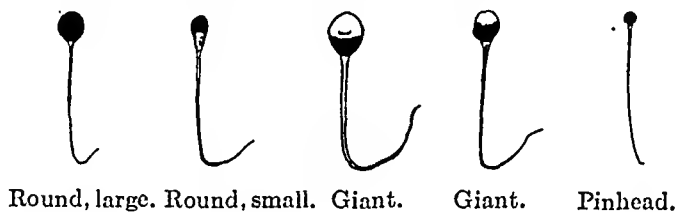
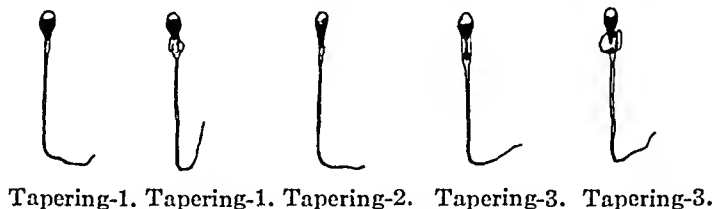
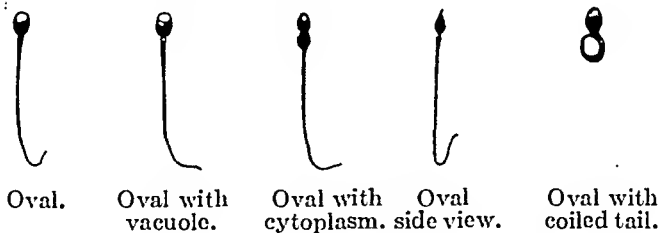


FIG. 13.—Per cent of oval spermatozoa.

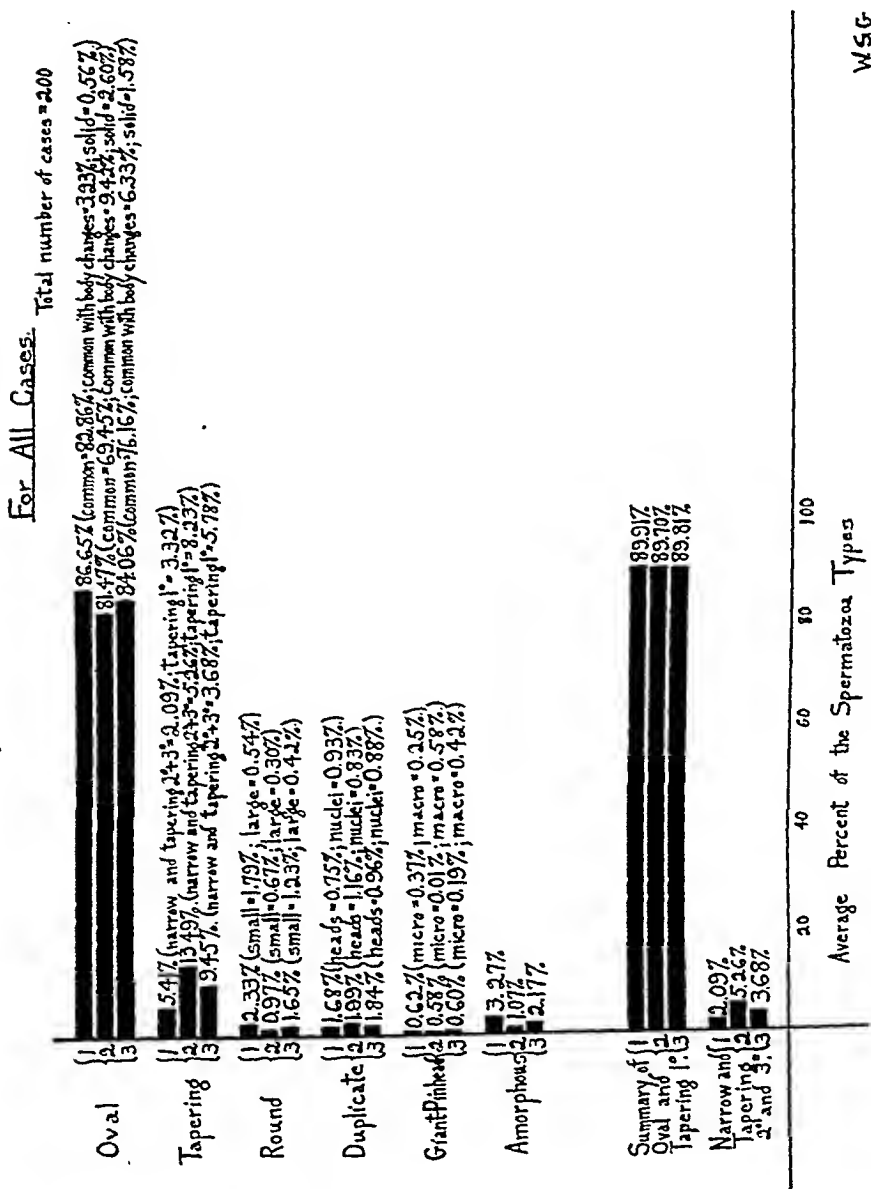
16.6%. Lagerlof⁷ reached similar conclusions after investigating the semen of 250 bulls. Woloskow,¹⁶ in an investigation on stallions, found that a foaling percentage of 89 was obtained where the abnormal cells were as high as 30%. McKenzie and Phillips⁹ estimated that the count of abnormal sperm in semen of boars should not exceed 10 to 15% for high fertility. McKenzie and Berliner⁸ have recently found that there is a seasonal variation in the percentage of abnormal forms in Shropshire rams. Ewes that were inseminated with semen during the off-season, when abnormal forms were as high as 84.8%, failed to become pregnant. When the percentage of abnormal forms dropped below 15%, all ewes inseminated with the semen conceived.

Moench¹³ adapted Williams and Savage's method of classification of sperm analysis. In 1931, he reported the results of his analysis

MORPHOLOGY OF SPERMATOZOA.



of 37 fertile normal men, and came to the conclusion that abnormal sperm heads never exceeded 19 to 20%. He assumed that fertility is impaired when abnormalities reach 20 to 22%, and that "clinical sterility" was usually present if 25% abnormal forms were found.



Morphology of the Spermatozoa.

Bar Graph A.

Kleegman⁶ reviewed the semen of 25 husbands of marriages where conception took place and normal children were born. Only in a single case was there an abnormal count as high as 25%.

On the other hand, Macomber and Saunders¹⁰ believe that information obtained from the cell count per cc. is as important as a study of the morphology of the sperm. They state that the "enumeration of spermatozoa gives identical information as to the fertility as does head measurement."

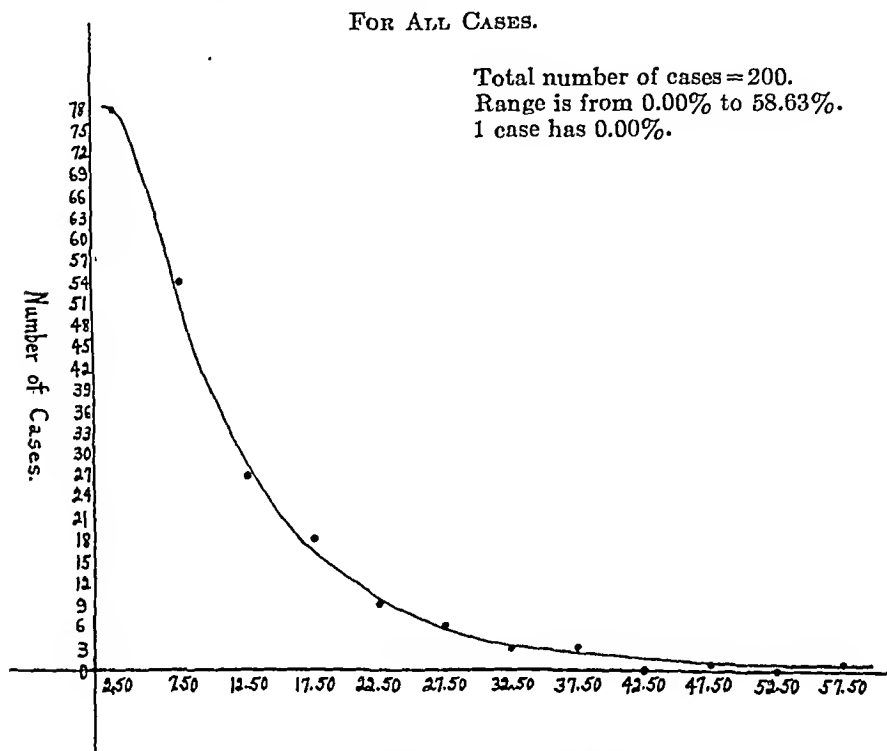


FIG. 14.—Per cent of all tapering types.

The time-consuming and complicated methods of accurately measuring the size of each sperm head did not seem practical or adaptable to clinical usage. Hence, the morphologic studies were done as follows:

A thin spread of semen was prepared on a clean glass slide. While still wet it was immersed in Schaudinn's solution to prevent distortion in drying. The preparation was then stained by eosin and hemotoxylin as described in a previous article by one of us.⁴

Three hundred or more cells were counted according to their morphologic type under oil-immersion magnification. The various types of cells were listed only as to their incidence or occurrence, and no preconceived opinions as to "normal" or "abnormal" cells were permitted. Six main types were thereafter recognized: 1, Oval; 2, Tapering; 3, Round; 4, Duplicate; 5, Giant and Pinhead; 6, Amorphous.

No word description can better the accompanying drawings to illustrate these types (Drawing A and Bar Graph A).

The various cells are quite distinctive in their shape and appearance.

The oval cells are far the most common cell type. Their average in the entire series of 200 cases was 84.06%, with a range from 31.36 to 98.23% (Fig. 13).

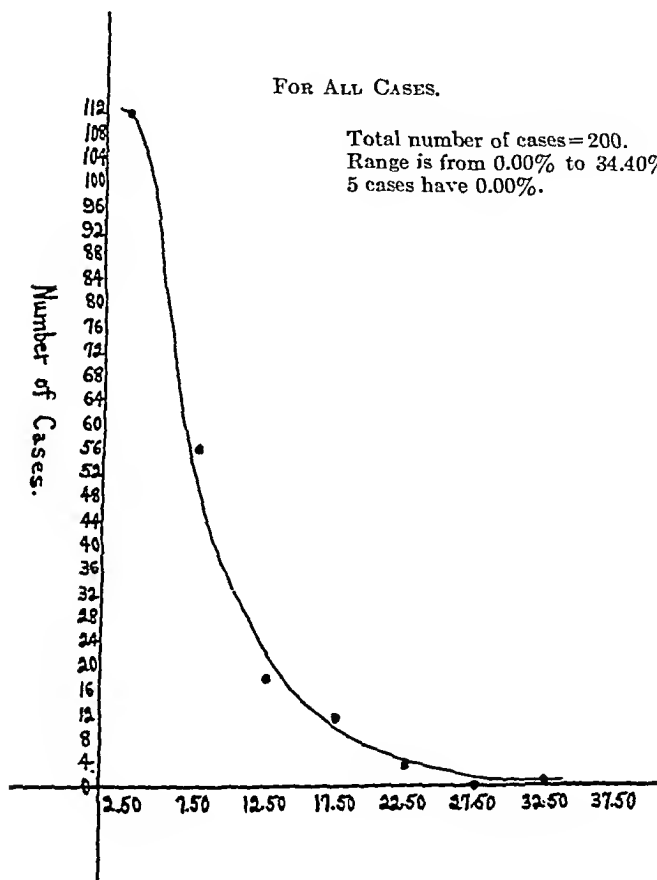


FIG. 15.—Per cent of tapering 1° spermatozoa.

Tapering cells were subdivided into 3 classes: Tapering 1, Tapering 2, and Tapering 3. There is no difficulty in differentiating the latter two types. Tapering 1, however, closely resembles the normal oval form. Grouping all tapering cells together, an average of 9.45% was obtained, with a range from 0 to 58.63% (Fig. 14).

If the Tapering 1 cells are considered alone, they are found to have an incidence of 5.78%, with a wide range of 0 to 34.4% (Fig. 15).

It is apparent that differences of opinion may exist between two or more observers, in distinguishing Tapering 1 cells from the usual oval type. (Note the discrepancy between Group I and Group II in Bar Graph A).

Because of their close resemblance, the Oval and Tapering 1 cells were classified together, and considered one and the same. A much more consistent agreement by the two laboratories was thus

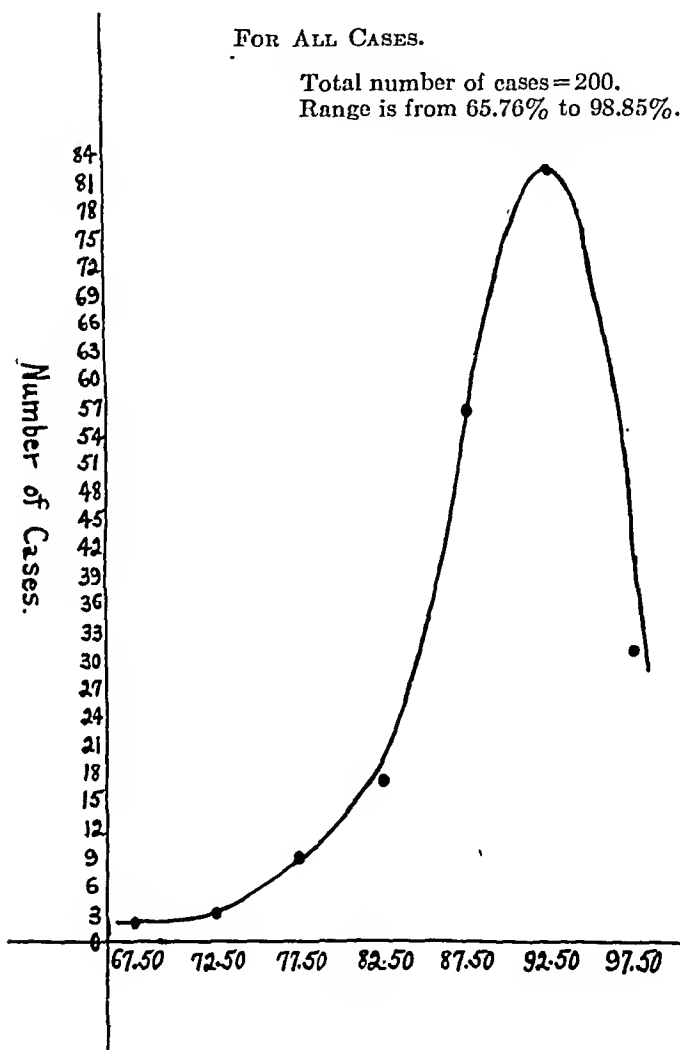


FIG. 16.—Per cent of oval and tapering 1° forms.

reached with an actual difference of only 0.2%. Under this plan, an average of 89.81% was found, with a range of 65.76 to 98.85% (Fig. 16).

If the Tapering 1 form is to be considered an abnormal cell, 3 of our cases would have 50% or more and 37 others 25% or more of atypical spermatozoa. On the other hand, if this cell is classified as normal and grouped with the Oval type, there were 5 cases with

FOR ALL CASES.

Total number of cases = 200.
Range is from 0.00% to 24.23%.
13 cases have 0.00%.

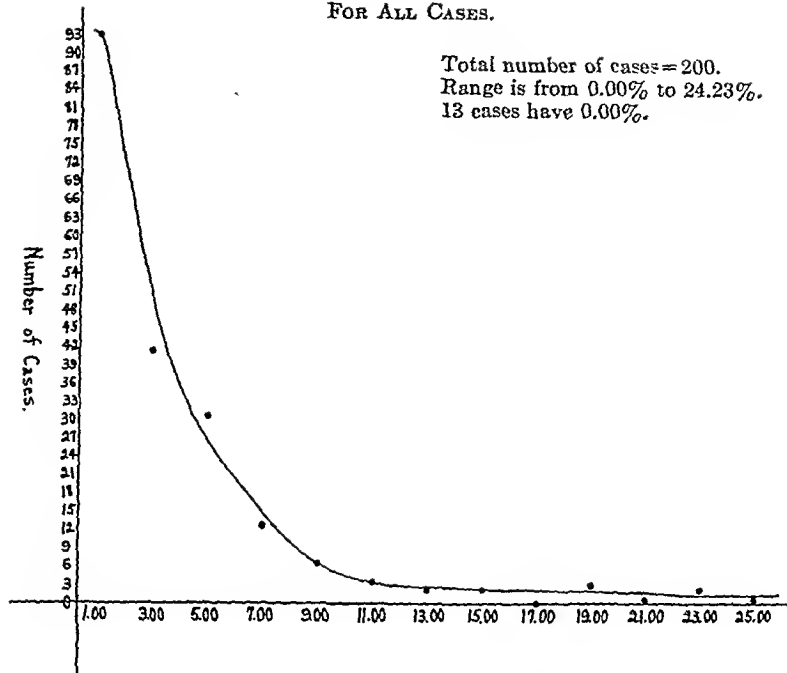


FIG. 17.—Per cent of narrow and tapering 2°+3° types.

FOR ALL CASES.

Total number of cases = 200.
Range is from 0.00% to 9.00%.
22 cases have 0.00%.

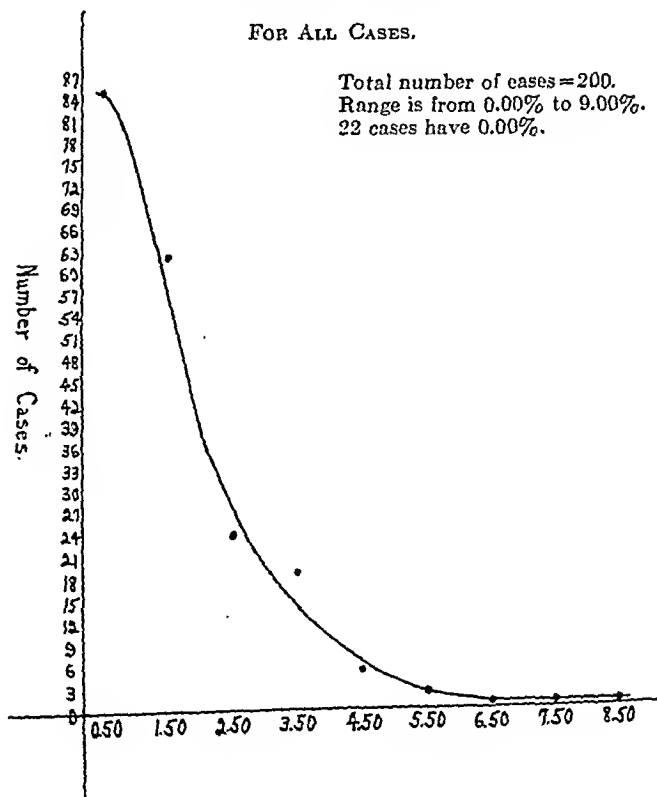


FIG. 18.—Per cent of round spermatozoa.

25% or more abnormal cells. In 1 case, 32.5% abnormal cells were found.

Unusual emphasis has been given herein to the discussion of the Tapering 1 cell because of the confusion regarding its classification. Statistically and morphologically, there seems no doubt that this rightfully should be considered an Oval spermatozoön.

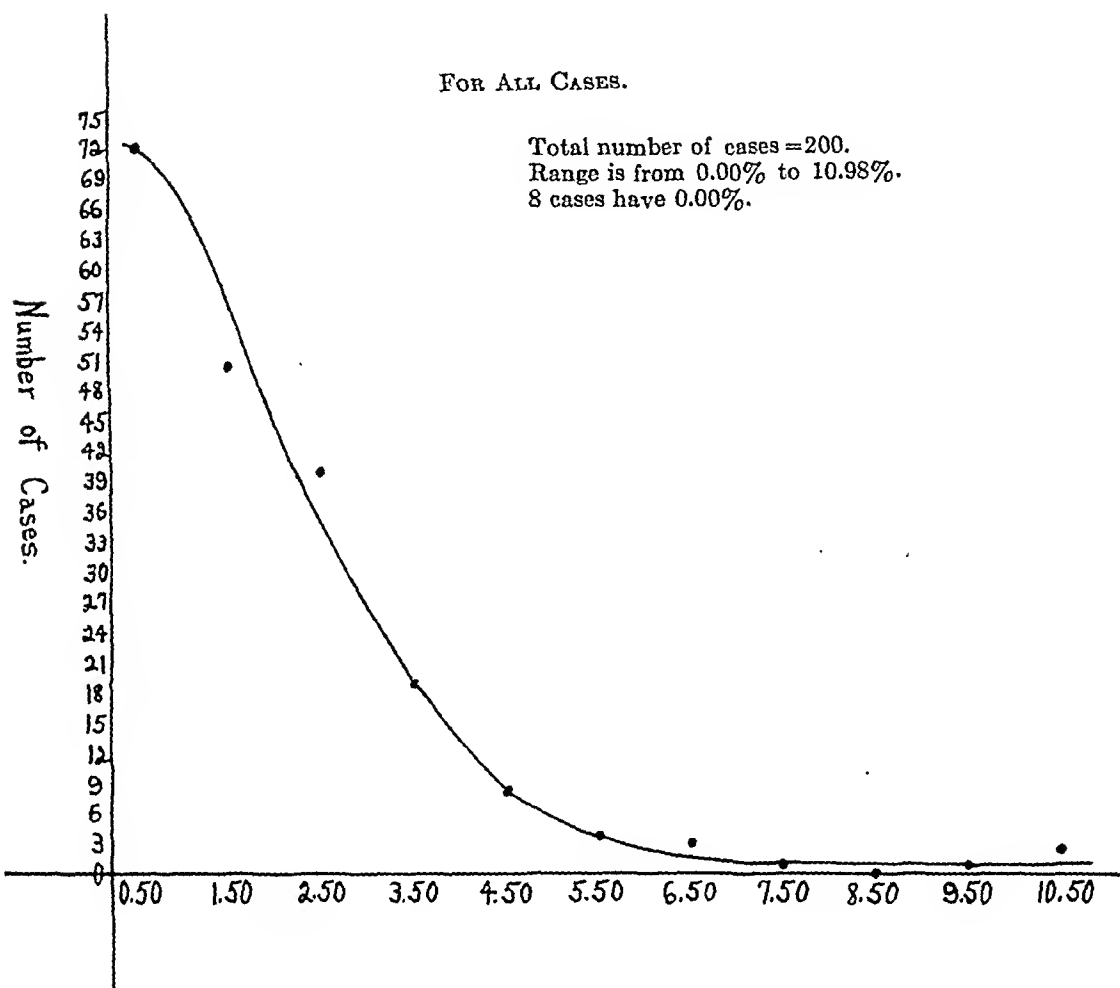


FIG. 19.—Per cent of duplicate spermatozoa.

If the Taperings 2 and 3 cells were grouped together with the narrow type (which may be side views of these), an average of 3.68% was obtained, with a range of 0 to 24.23% (Fig. 17).

The above findings are at variance with Moench's limit of 8.5% for fertile specimens. In 11% of our cases these cell types were present beyond that figure.

Round forms were comparatively rare, having an incidence of 1.65%, and a range from 0 to 9% (Fig. 18).

Duplicate cells comprised double nuclei, double heads, or double

FOR ALL CASES.

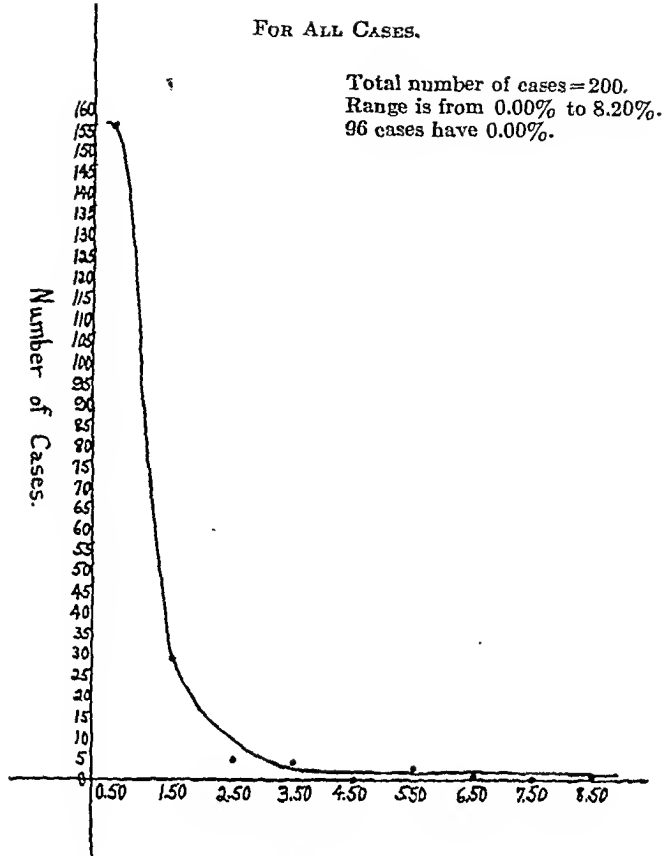


FIG. 20.—Per cent of giant and pinhead spermatozoa.

FOR ALL CASES.

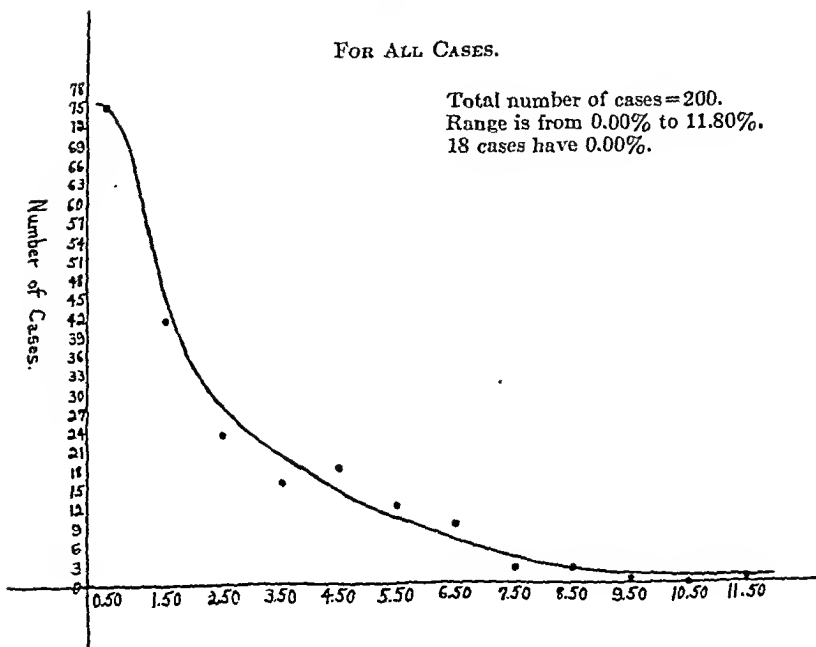


FIG. 21.—Per cent of amorphous spermatozoa.

tails. They averaged as a group 1.84%, and had a range from 0 to 10.98% (Fig. 19).

The Giant and Pinhead groups occurred most rarely, having an average of 0.6%, with a range of from 0 to 8.2% (Fig. 20).

The Amorphous group, so-called because their unusual varieties in shape defy any appropriate name, had an average of 2.1%, with a range of 0 to 11.8% (Fig. 21).

Summary and Conclusions. 1. Detailed analyses of the semen of 200 fertile men whose wives were in the first half of gestation are herein reported.

2. The volume of ejaculate averaged 3 cc. when collected by withdrawal, and 2.3 cc. by condom.

3. When motility is satisfactory a determination of the pH of semen is unnecessary.

4. Estimation of the sugar content of semen has no apparent clinical value.

5. Motility is apt to be impaired when the condom is used for collection.

6. A method of appraising motility is discussed.

7. No relationship was demonstrated between the grade of motility of the spermatozoa and the age of the men.

8. Spermatozoa counts averaged 120,530,000 per cc.

9. Twenty-five per cent of the cases had spermatozoa counts below 60,000,000 per cc.

10. No constant relationship exists between the amount of ejaculate and the spermatozoa count per cc.

11. Larger ejaculates usually have higher total cell contents.

12. Specimens with high cell counts generally exhibit better motility.

13. Differential morphologic counts were done on each specimen.

14. Oval cells, including Tapering 1, averaged 89.81%.

15. If Tapering 1 is to be considered an abnormal cell, 3 of our cases would have 50% or more, and 37, 25% or more atypical spermatozoa.

16. Since Tapering 1 cell so closely resembles the oval form, we believe they should be classed together.

17. Taperings 2 and 3 averaged 3.68%, but in 22 of the cases they were found in excess of 8.5%.

18. From previous clinical experience and investigative study, it is the opinion of the authors that an assay of fecundity includes a consideration of volume, grade of motility, number of spermatozoa and percentage of abnormal forms. The fertilizing value of semen depends on a combination of all four of these basic factors, rather than any single one alone.

The generosity of the National Research Council permitted the equipping of a laboratory and the defrayal of expenses for the portion of the investigation carried on at the New York Hospital.

Miss Frances E. Scudder, B.S., most ably conducted the laboratory analyses at the New York Hospital.

The authors wish to express their sincere appreciation for the invaluable assistance of Mr. William S. Goldfarb, M.S., B.S., for his expert summary and arrangement of the biometric statistics.

The coöperation of Miss Jessie Stewart Ross, Social Service, Bellevue Hospital, is most deeply appreciated.

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VITAMIN C IN THE SPINAL FLUID.

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WE^{9a} have recently suggested that vitamin C may play a rôle in the metabolism of nervous tissue and presented the following evidence:

1. It is present in the cerebrospinal fluid.
2. The adrenal, brain and pars intermedia of the hypophysis (all nervous tissues) contain large amounts of vitamin C.
3. Clinical alcoholic conditions association with neural or mental changes have subnormal vitamin C levels in the blood and spinal fluid, whereas chronic alcoholics without neural or mental changes tend to have normal vitamin C levels in the blood and spinal fluid.^{9b} Whether vitamin C is a major factor in these changes is not as yet clear and hardly seems likely. The findings do, however, suggest that there is a large nutritional factor in the production of nervous and mental changes in alcoholics.
4. Vitamin C has definite protective and therapeutic value in experimental poliomyelitis (Jungeblut^{4a, b}).

5. Pathologically (Davison¹), the peripheral nerves of animals placed on a vitamin C-free diet showed slight disintegration of myelin and on rare occasions, destruction of the axis cylinder. In addition, the various nerve cells, especially the anterior horn cells, showed vacuolization, liquefaction necrosis, swelling and pyknosis. He, however, noted similar changes in guinea pigs that were totally starved and was therefore unwilling to attribute the changes noted to avitaminosis C.

6. Guinea pigs deprived of vitamin C became nervous and apprehensive (Meyers and McCormick⁵). They responded violently to the slightest noise, running wildly about the cage until they fell exhausted. We have been able to confirm these results in every detail.

It would therefore seem a matter of paramount importance not only to study the metabolism of this vitamin in the brain, but to establish some standards for normality regarding the presence of this vitamin in the spinal fluid.

Methods and Materials. Determinations of vitamin C in both the blood and spinal fluid were carried out on 257 patients. Half of the patients were from the psychiatric wards (including 130 alcoholics previously reported) and the others were from the medical and neurologic wards. No attempt was made to group these cases diagnostically—they were all, however, afebrile. Because of the large number of alcoholics and because the patients at this hospital are in general drawn from the lowest income groups, subsisting usually on diets low in all vitamins, there is a very high incidence of subnormal nutritional states in our material.

The specimens of spinal fluid and oxalated blood from each patient were taken immediately to the laboratory and titrated by the method of Farmer and Abt.²

We have regarded 0.70 mg. % as the lower limits of normal vitamin C in the blood plasma. This is the figure given for this method by Farmer and Abt,² Wright,¹⁰ and Greenberg, Rhinehart and Phatak.³ Determinations made by us on 14 healthy medical students and internes ranged from 0.74 to 1.38 mg. %.

Plaut and Bulow have set as normal standards for spinal fluid the following figures for the 20- to 35-year-age group, 1.77 mg. %; 36- to 59-year-age group, 1.97 mg. %; 61- to 83-year-age group, 0.51 mg. %. They do not state, however, what their criteria of normality are.

In a previous paper we⁷ attempted to establish normal limits for the vitamin C content in the spinal fluid. We regarded as normal in spinal fluid those patients who had both normal bloods and a normal response to the 5-hour urinary excretion test of Wright.^{8*} Of 133 patients studied, 26 fulfilled these criteria. Their spinal fluids ranged from 1.82 to 4.18 mg. % of vitamin C. In the present paper, we have considered 1.82 mg. % as the lower limit of normal cevitic acid content of the spinal fluid.

* Wright's test consists in determining the total 5-hour urinary excretion of vitamin C following an intravenous test dose of 1 gm. of crystalline cevitic acid. A 5-hour excretion of 400 mg. or more of cevitic acid is considered normal.

After we had submitted this paper for publication a new photo-electric method of titrating vitamin C was published.* The authors of this paper claim that the method of Farmer and Abt, used by us in titrating spinal fluid, yields figures for vitamin C that are too high. However, in a previous study,⁷ we have shown that a close parallelism exists between our blood and spinal fluid figures. Therefore, although our absolute numerical figures for vitamin C in the spinal fluid may be incorrect, we feel that their relationship to our blood vitamin C values is correct, and that consequently our conclusions are valid.

Plaut and Bülow^{6a,b} reported losses of as high as 90% of the reducing power of the ascorbic acid in the spinal fluid on standing 1½ hours at room temperature, but state that it retains three-fourths of its reducing power if acidified with 0.1 cc. of trichloroacetic acid to each cubic centimeter of spinal fluid. In our own determinations, we found a consistent average loss of reducing power against sodium 2:6 dichlorophenol-indophenol of only 10% in 1 hour without acidification and only a negligible loss if the spinal fluid were acidified immediately.

Results. In analyzing our material we have divided our patients on the basis of blood vitamin C levels into 3 groups: 1, *Normal*, with blood levels of 0.7 mg. % or more; 2, *Intermediate subnormal*, with a blood vitamin C level of 0.4 to 0.69 mg. %; and, 3, *Low*, with blood vitamin C of less than 0.4 mg. %.

In the normal blood group (Graph 1) there are 42 cases. Of these, the spinal fluid is normal (1.82 mg. % or more) in 36 (86%). The average spinal fluid for the group is 2.40 mg. % of vitamin C.

In the intermediate subnormal blood group (Graph 1) there are 64 cases. Of these, the spinal fluid vitamin C is normal in 30 (47%) and low (below 1.82) in 34 (55%). The average spinal fluid value for the whole group is 1.81 mg. %.

In the low blood group (Graph 2) there are 151 cases. Of those, the spinal fluid is low (below 1.82) in 137 cases (91%). The average spinal fluid value for the group is 0.97 mg. % of vitamin C.

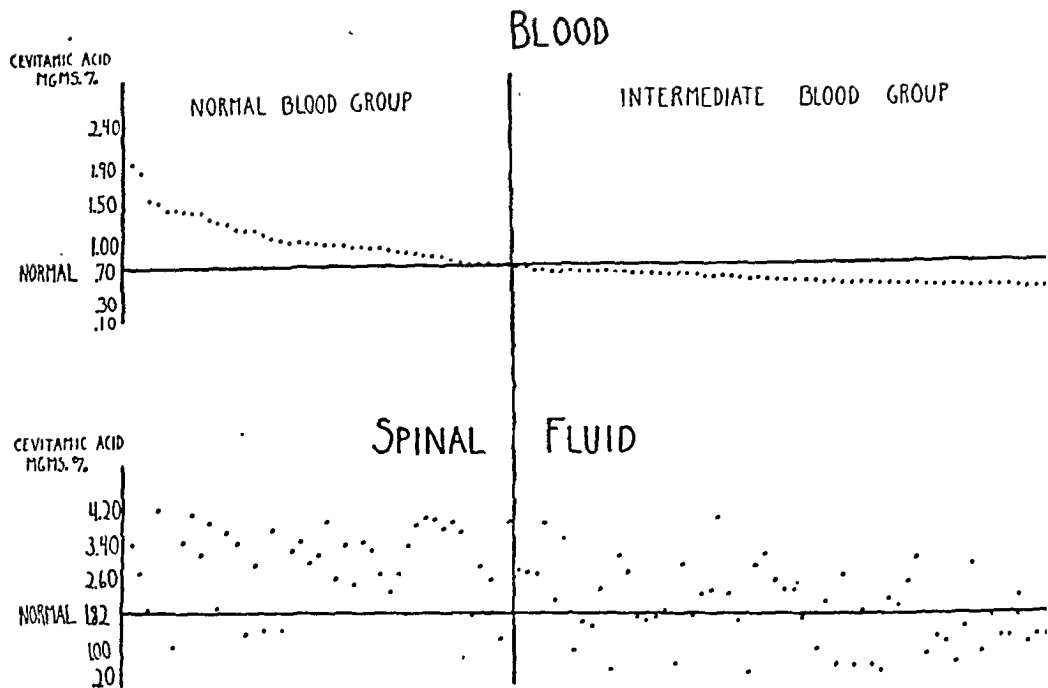
In Table 1, 248 cases in which the age was known are arranged by age groups (using the groupings of Plaut and Bulow).

Discussion. We believe that the results given above show that both a normal blood ascorbic acid (above 0.7 mg. %) and a very low blood vitamin C (below 0.4 mg. %) are almost invariably associated with correspondingly normal and subnormal values for the spinal fluid.

In the intermediate subnormal range no such close correlation exists. (In a previous paper⁷ we demonstrated similar relationships with the urinary excretion test.)

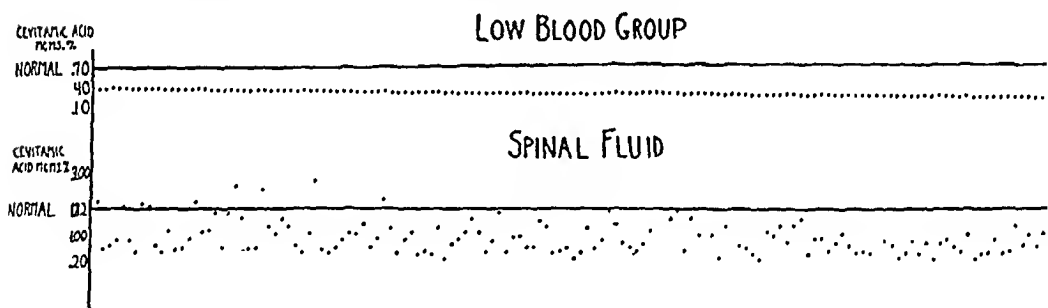
Our results show no significant age correlation in the level of vitamin C in the blood or spinal fluid. There is a slight drop in the

* Pijoan, M., Alexander, L., and Wilson, A.: J. Clin. Invest., 17, 169, 1938.



GRAPH 1.—Spinal fluid correlations in patients with normal and moderately sub-normal (intermediate) blood cevitic acid.

This and the following graph are drawn in descending order of blood cevitic acid. Each pair of dots on the same ordinate in the two halves of the graph represents simultaneous blood and spinal fluid determinations on the same patient.



GRAPH 2.—Spinal fluid correlations in patients with low blood cevitic acid.

TABLE 1.—SPINAL FLUID CEVITAMIC ACID BY AGE GROUPS.

Age group.	No. of cases.	Spinal fluid vitamin C. (mg. %).	
		Range.	Av. value.
0-19	5	0.92-4.18	1.74
20-35	69	0.46-3.96	1.59
36-60	138	0.36-3.96	1.54
61-83	36	0.28-4.07	1.27

TABLE 2.—NORMAL SPINAL FLUID CEVITAMIC ACID BY AGE GROUPS.

Age group.	No. of cases.	Spinal fluid vitamin C, av. value (mg. %).
0-19	2	3.73
20-35	21	2.92
36-60	49	2.64
61-83	7	3.05

spinal fluid cevitic acid in the 61- to 83-year-old-age group. This is not present if only the normal spinal fluids are tabulated (Table 2). These findings are at variance with those previously reported by Plaut and Bülow^{6a} and deserve further study.

Conclusions. 1. There is a close correlation between the blood and spinal fluid levels of vitamin C in the ranges stated.

2. There is no significant age correlation in the spinal fluid cevitic acid of adults, although there is a slight drop in the group above 61 years of age.

3. It is probable that vitamin C plays a rôle in nervous tissue metabolism, although the mechanism of this action is not as yet determined.

We are indebted to Drs. Karl M. Bowman, Foster Kennedy and I. Ogden Woodruff for the use of clinical material from their respective services at Bellevue Hospital.

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NOTE ON THE LACK OF CORRELATION OF CAPILLARY FRAGILITY WITH VITAMIN C CONTENT OF BLOOD, SPINAL FLUID AND URINE.

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At the present time, tests of capillary fragility are commonly used to determine the presence of "subclinical scurvy" associated with lowered vitamin C reserves. The reliability and actual relation of such tests as indices of vitamin C nutrition has been both affirmed^{5,6,8,10,13,14,19} and denied^{1,2,11,12} by various investigators.

In the course of studies on the relationship of vitamin C in the blood, spinal fluid and urine^{16,17} we performed, in addition to chemi-

cal titration of the cevitic acid, tests of capillary fragility on 88 patients on whom we had determined the blood vitamin C. In 78 of these the spinal fluid vitamin C was also determined and in 75 the urinary excretion following an intravenous test dose.

Methods. The capillary resistance and fragility was tested by two methods: 1, Wright's modification of the Rumpel-Leeds test,¹⁹ and, 2, Dalldorf's suction cup method.⁵ In all but 4 patients, who refused to cooperate in the rather uncomfortable Rumpel-Leeds test, both tests were done.

In Wright's modification of the Rumpel-Leeds test, a blood pressure cuff is applied to the arm and kept inflated for 15 minutes, one-half way between systolic and diastolic pressure. Five minutes after release of the cuff, the number of petechiæ in a 2.5 cm. circle drawn on the flexor surface of the forearm are counted. Wright considers 0 to 10 petechiæ normal and 10 to 20 borderline. For the sake of simplifying analysis, we have charted as "normal" all cases with 15 petechiæ or fewer.

In Dalldorf's method, a 1 cm. suction cup is applied to the skin of the upper arm near the deltoid insertion and varying negative pressures are applied for 1 minute. If petechial hemorrhage is produced at 25 cm. negative Hg pressure or below, the capillary fragility is regarded as abnormal (see discussion).

The vitamin C assays in the blood, spinal fluid and urine were done by the method of Farmer and Abt.⁷ We regard as normal blood levels of 0.7 mg. % or over^{2,7,9,16} and spinal fluid levels of 1.82 mg. % or over. After we had submitted this paper for publication a new photo-electric method of titrating vitamin C was published.* The authors of this paper claim that the method of Farmer and Abt, used by us in titrating spinal fluid, yields figures for vitamin C that are too high. However, in a previous study,⁷ we have shown that a close parallelism exists between our blood and spinal fluid figures. Therefore although our absolute numerical figures for vitamin C in the spinal fluid may be incorrect, we feel that their relationship to our blood vitamin C values is correct, and that consequently our conclusions are valid. In studying the urinary excretion, the 5-hour test of Wright²⁰ was used in which in normal individuals 400 mg. or more of cevitic acid are excreted in 5 hours following a 1 gm. intravenous test dose.

The patients used in this study were divided about equally between the neuro-psychiatric and general medical wards of this hospital. No attempt was made to select cases on a basis of either disease entities or dietary history. It should be noted, however, that the patients at Bellevue are in general drawn from the lowest income groups in the population and that consequently in our material there is a preponderance of low vitamin C levels.

Results. (See Charts 1 and 2.) To summarize, we find when the blood vitamin C is normal, the Rumpel-Leeds test is normal in about three-fourths of the cases (74%) and when the blood is either moderately subnormal or definitely low, the Rumpel-Leeds is abnormal in 70%. In other words, there is about 70 to 75% agreement between the blood vitamin C and the Rumpel-Leeds tourniquet test as standardized by Wright.

As the accompanying charts show, there was little correlation

* Pijoam, M., Alexander, L., and Wilson, A.: *J. Clin. Invest.*, **17**, 169, 1938.

between Wright's modification of the Rumpel-Leeds test and the spinal fluid and urinary excretion assays of cevitamic acid.

If with the Dalldorf suction cup method 30 cm. Hg negative pressure is used as the lower limit of normal,* the test was found to have very little correlation with the actual vitamin assay.

As Charts 1 and 2 show, the incidence of "abnormal fragility" tests in the group of cases with normal vitamin C stores is too high and, conversely, the incidence of normal fragility in the cases with low vitamin C reserves is too frequent to make negative pressure tests, as used by us, of any clinical value.

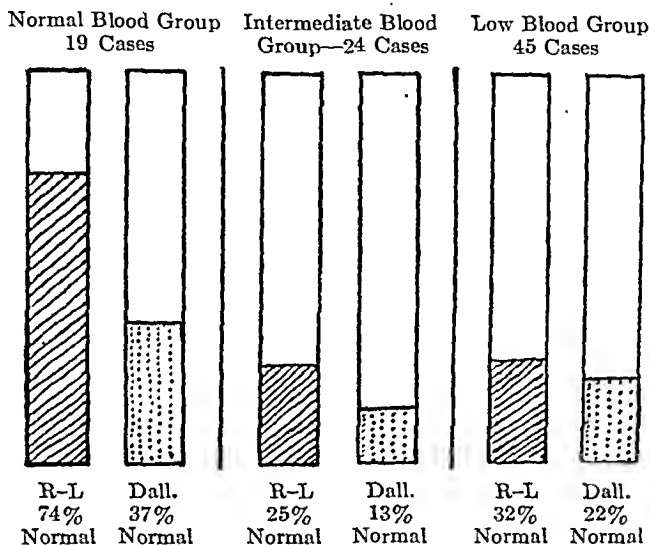


CHART 1.

It should be noted that both Wright and Dalldorf emphasize that single determinations are not of as much significance as a rise in the capillary resistance following vitamin C therapy. With this point of view we are in entire agreement. Dalldorf, indeed, in his published studies has never, except by implication, stated that there was any one level which could be taken as definitely abnormal. However, in a personal communication, he has stated that he believed a positive hemorrhagic reaction at 25 cm. Hg negative pressure probably was abnormal.

There was one observation that we made in using the Dalldorf

* We recalculated our results, using 20 cm. and 15 cm. of negative Hg pressure as lower limits of normal. Taking these values of normal, the results with the Dalldorf test are no better. For example, using 15 cm. Hg as the lower limit of normal, we find that there are 58% normal Dalldorf tests in the normal blood vitamin C group but that there then are (on this basis) 37% normal Dalldorf tests in the sub-normal blood vitamin C group—a correlation still too poor to be of any clinical value. We also found that there was no significant change in the results if only tests with grossly confluent hemorrhage were considered as positive.

apparatus that we feel is worth mentioning. In 14% of our cases we found that with the suction cup a reaction that at lower negative pressures was positive, would be negative at high negative pressures, *e. g.*, hemorrhage could be produced at 35 cm. Hg negative pressure and not at 50 cm. We attribute this to complete shutting off of capillary flow at the rim of the cup at high negative pressures.

Finally, we wish to emphasize that there are other causes* than vitamin C deficiency of increased capillary fragility, and that abnormally high fragility should be attributed to vitamin C deficiency only if the vitamin C is low prior to therapy and if the abnormal state of fragility disappears following adequate vitamin C therapy.

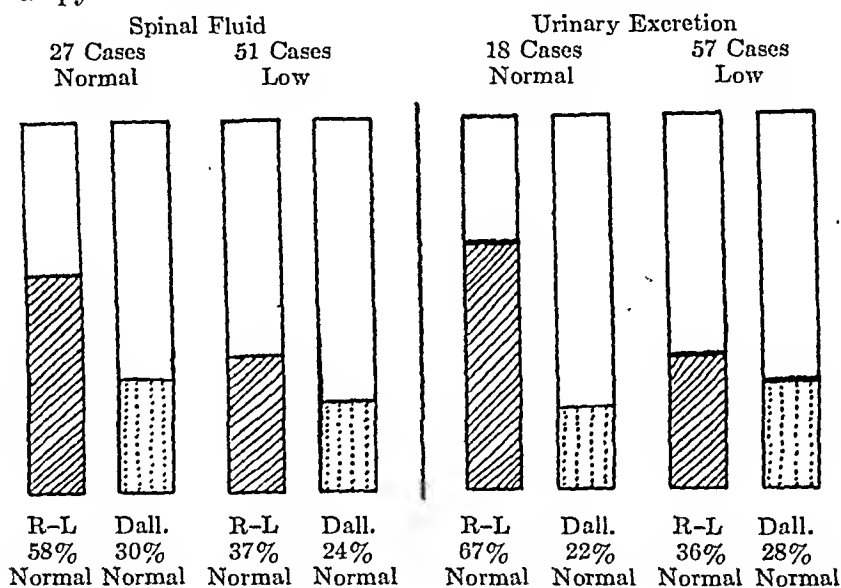


CHART 2.

Conclusions. 1. Clinical tests of capillary fragility may be normal in the presence of markedly low values for vitamin C in blood, spinal fluid and urine and conversely abnormal in the presence of normal C values.

2. The suction cup negative pressure method in our hands produced petechiæ at 25 cm. Hg in 63% of our normal cases and is, therefore, when used in this fashion, of little value in estimating vitamin C deficiency.

3. The Rumpel-Leeds test as standardized by Wright showed some correlation with blood vitamin C levels but not with spinal fluid or urinary excretion tests of vitamin C.

* The following other conditions have been listed as responsible for abnormal capillary fragility:¹⁸ thrombocytopenic purpura, hemophilia, neoarsphenamine, and other drugs; anaphylactoid purpura, acute nephritis, carbon monoxide poisoning, toxins, *e. g.*, diphtheria, scarlet fever, acute infections; acetonia, menstruation, anemia, other vitamin factors, particularly vitamins P and D,^{3,4,15} and a large group of cases in which the etiology is not apparent but which are certainly due to factors other than vitamin C.

4. If indirect methods of determining vitamin C must be used, Wright's modification of the Rumpel-Leeds test is the preferable method. The limitations of this test, however, must be understood.

5. Abnormal fragility tests should be considered as being due to vitamin C deficiency only if: *a*, the vitamin C in the body fluids is low; and, *b*, if the fragility returns consistently to normal following adequate vitamin C therapy.

We wish to thank Drs. I. Ogden Woodruff, Foster Kennedy, Karl M. Bowman, respectively, Directors of the First Medical, Neurological and Psychiatric Divisions of Bellevue Hospital for the use of clinical material from their wards.

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NOTE ON THE LACK OF HEMOREGULATORY EFFECT OF ASCORBIC ACID ON PATIENTS WITH POLYCYTHEMIA VERA.

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It has been postulated by Barron that one of the functions of ascorbic acid is to maintain the hemoglobin concentration in the blood at its normal level. This hypothesis is supported by two facts. First, the decreased hemoglobin content in early stages of scurvy occurs before clinical symptoms appear; and the hemoglobin comes back to normal after the administration of ascorbic acid before these symptoms subside.^{3,4} Second, cobalt polycythemia is prevented in rabbits when ascorbic acid and cobalt are given simultaneously.¹ Furthermore, ascorbic acid on oxidation reduces

ferrihemin to ferrohemin,² and hemoglobin results from the combination of ferrohemin and globin.

The power of ascorbic acid to control the appearance of cobalt polycythemia in rabbits suggested its use in the treatment of polycythemia vera. At Dr. Barron's suggestion, ascorbic was administered to several cases of polycythemia vera.

The first patient tested was an elderly man with a consistently high erythrocyte count and a peculiar violaceous color of his skin. He was treated while in the Billings Memorial Hospital, where he was on the service of Dr. G. F. Dick. There was some question about the correct diagnosis in this instance, so that the failure of the ascorbic acid to influence the erythrocyte count was more or less discredited. It was also felt at that time that if the erythrocyte count were brought down to normal levels the ascorbic acid might be more likely to maintain it there. Three such cases were then studied, brief synopses of which follow:

Case Abstracts. CASE 1. A 50-year-old mulatto woman had been under treatment for 3 months for typical polycythemia vera, associated with hypertension. She had been given increasing doses of acetylphenylhydrazine hydrochloride until she was taking 0.2 gm. daily. After 10 days of this her erythrocyte count began to decline rapidly (Table 1) and she was hospitalized. As the blood count returned towards normal, the administration of 400 mg. of ascorbic acid daily was started. After 7 months there has been no apparent protection against the recurrence of polycythemia.

TABLE 1.—THE BLOOD PICTURE IN CASE 1.

Date.	Hemoglobin, gm. %.	Erythrocytes, millions per mm. ³	Comment.
2/23/37	26.2	9.30	Acetylphenylhydrazine
3/18	26.4	7.87	
4/1	26.2	9.24	
4/15	24.2	7.99	No medication
4/29	27.0	8.48	Acetylphenylhydrazine, 0.1 gm. b.i.d.
5/10	16.6	5.60	
5/15	Hospitalized
5/17	10.8	3.44	
5/24	8.3	2.99	
5/27	8.2	2.95	Ascorbic acid, 400 mg.
6/3	10.6	3.49	
6/10	11.7	4.13	
6/17	14.3	4.85	
6/24	14.9	4.90	
6/30	15.7	5.04	Discharged from hospital; vitamin C continued
7/13	16.2	5.20	
7/20	18.4	5.85	
12/	25.0	7.64	Ascorbic acid stopped

CASE 2. A 57-year-old white woman had been under the care of one of us (E. V. K.) for 2 years for the control of classical polycythemia vera. At first, a solution of potassium arsenite was used satisfactorily, but when she became intolerant of it, acetylphenylhydrazine was given. At our suggestion she entered the hospital for experimentation. The dosage of acetylphenylhydrazine was increased steadily until the red blood count fell to just below normal (Table 2). At this time, 400 mg. of ascorbic acid was

given instead of the acetylphenylhydrazine. It is not possible to estimate any protection against the development of further anemia. After 4 weeks, because of a steady increase of the erythrocytes, the vitamin was discontinued.

TABLE 2.—THE BLOOD PICTURE IN CASE 2.

Date.	Hemoglobin, gm. %.	Erythrocytes, millions per mm. ³	Comment.
6/4/34	22.4	6.57	Solution of potassium arsenite
10/16	18.0	5.33	
11/19/36	27.9	7.45	
12/17	23.7	6.52	Acetylphenylhydrazine
2/13/37	4.20	
7/2	21.9	7.88	Hospitalized, drug dose increased
7/5	
7/8	24.3	7.69	
7/16	21.8	6.64	
7/26	21.6	5.97	
8/2	19.0	5.47	
8/9	16.3	5.01	
8/13	Ascorbic acid, 400 mg., replaces acetylphenylhydrazine
8/16	13.5	4.13	
8/23	12.0	3.45	Discharged; vitamin C continued
8/30	12.7	3.75	
9/16	18.2	4.97	Ascorbic acid stopped
9/20	20.2	6.33	Acetylphenylhydrazine
10/18	4.80	

CASE 3. A 46-year-old white man entered the hospital at our request for the management of an untreated case of typical polycythemia vera. His erythrocytes were decreased by daily venesection. A total of 4500 cc. of blood was removed in 6 days. Ascorbic acid was given in daily doses of 400 mg. after the second day in the hospital. Four weeks after the last bleeding the vitamin was discontinued because of a steady increase of the erythrocytes (Table 3).

TABLE 3.—THE BLOOD PICTURE IN CASE 3.

Date.	Hemoglobin, gm. %.	Erythrocytes, millions per mm. ³	Comment.
9/2/37	26.4	8.35	Hospitalized
9/3	
9/4	22.0	9.00	
9/7	20.7	6.79	Ascorbic acid, 400 mg., started; venesections started
9/10	16.6	4.91	
9/11	Venesection stopped
9/13	15.0	4.85	
9/15	14.8	4.89	Discharged; vitamin C continued
10/5	16.4	5.72	
10/21	18.2	6.50	Ascorbic acid stopped
11/11	16.0	5.66	Acetylphenylhydrazine
12/16	15.2	5.19	

Two outpatients, suffering from characteristic polycythemia vera, whose blood counts had been well controlled by acetylphenylhydrazine, were given instead 400 mg. of ascorbic acid daily. Their blood counts promptly increased and the vitamin was withdrawn.

Summary and Conclusions. 1. An attempt has been made to discover whether ascorbic acid is capable of maintaining the erythrocyte counts of patients with polycythemia vera at normal levels.

2. Ascorbic acid seems to have no influence, either good or bad, on the red blood counts and the hemoglobin levels of such patients, especially in preventing the return to polycythemic levels.

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RELIEF OF ANGINOID PAIN FOLLOWING REMOVAL OF INTRATHORACIC NON-TOXIC NODULAR GOITER.*

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VARIOUS aspects of the relationship between the thyroid gland and cardiac disorders have been studied and discussed in detail in the literature. These include: (a) the effect of total ablation of the normal thyroid upon congestive heart failure and angina pectoris; (b) the relationship between thyrotoxicosis and congestive heart failure, cardiac arrhythmias, and angina pectoris; and (c) the relationship between "non-toxic" goiter and certain cardiac abnormalities. One aspect of the general problem, however, has received comparatively little attention, namely the relationship between substernal "non-toxic" goiter and anginoid pain.

Bisgard¹ in 1936 reported the case of a 67-year-old man with a large nodular substernal goiter of long standing, who had exhibited effort angina for 2 years. The basal metabolic rate was -32% ; glucose tolerance was somewhat impaired; blood cholesterol was 173 mg. %, and the electrocardiogram was normal. After subtotal thyroidectomy the attacks of pain disappeared promptly, the basal metabolic rate rose to normal, and glucose tolerance improved. Bisgard suggested that interruption of possible direct nervous communication between the heart and the thyroid, in the adventitia of the aorta, carotid, innominate or thyroid arteries, might have produced the relief of pain in his patient.

Kreuzfuchs² recently described what he calls "thyreoptotic pseudo-angina pectoris" and states that he had mentioned it as early as 1912. He believes that anginoid pain, without true heart disease, may be associated with "ptosis" of a normal thyroid isthmus or with intrathoracic goiter, especially in the fifth and six decades;

he ascribes the symptoms to pressure upon the aorta, or to displacement of the trachea and cardiac plexuses. He considers irradiation the treatment of choice,* but states that in some cases the symptoms subside spontaneously after the age of 50.

In connection with these reports, the following case is of interest.

Case Report. R. S., a married Jewish woman, aged 45, was first seen by one of us on November 13, 1935. She had been in good health, except for slight dyspnea on effort, until the evening of October 24, 1935. While sitting quietly at home, she was suddenly seized with a sense of tightness and pressure in the left upper chest, left shoulder, the left side of the back to the waist, the inner side of the left arm to the elbow and the left lower jaw. The sensation was extremely severe and did not start at one spot and radiate, but appeared simultaneously in the above mentioned areas, and was associated with difficulty in respiration. The symptoms lasted about 5 minutes and left her in a weakened condition. A few minutes later, she had another seizure of a similar nature, and her family physician was called. Except for a rise in blood pressure of 40 mm. Hg and tachycardia, nothing of significance was found on examination. There was no cyanosis, cough, hoarseness, sweating or chilliness associated with the attack. This seizure, however, lasted about an hour.

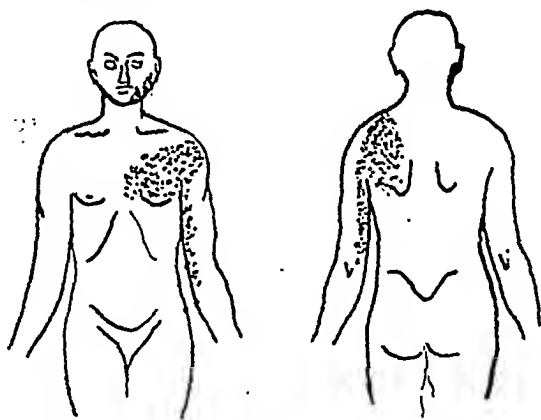


FIG. 1.—Distribution of pain during attacks.

During the following 3 weeks, the attacks recurred with great similarity of symptoms and time of onset. Usually, the seizures came on while at rest in bed, and awakened her from sleep between 4 and 5 A.M., whereupon she would get out of bed, walk about, and the attack would stop. One attack, however, lasted from 7 P.M. to 7 A.M. She was not aware of any exciting cause of the seizures; walking seemed to relieve the pain rather than induce it. Her past medical and family histories were unimportant.

On *physical examination*, she had the appearance of good health, was short and slightly overweight. There was no apparent dyspnea, cyanosis or jaundice. Her blood pressure was 120/80, and physical examination was negative except for diseased tonsils and dental caries. No thyroid enlargement could be detected in the neck. Fluoroscopy, however, disclosed a mass in the superior mediastinum, apparently substernal thyroid resting upon the aorta. The orthodiagram disclosed the heart to be of

* There is little evidence that the non-toxic thyroid is affected structurally or functionally by irradiation in therapeutic dosage.

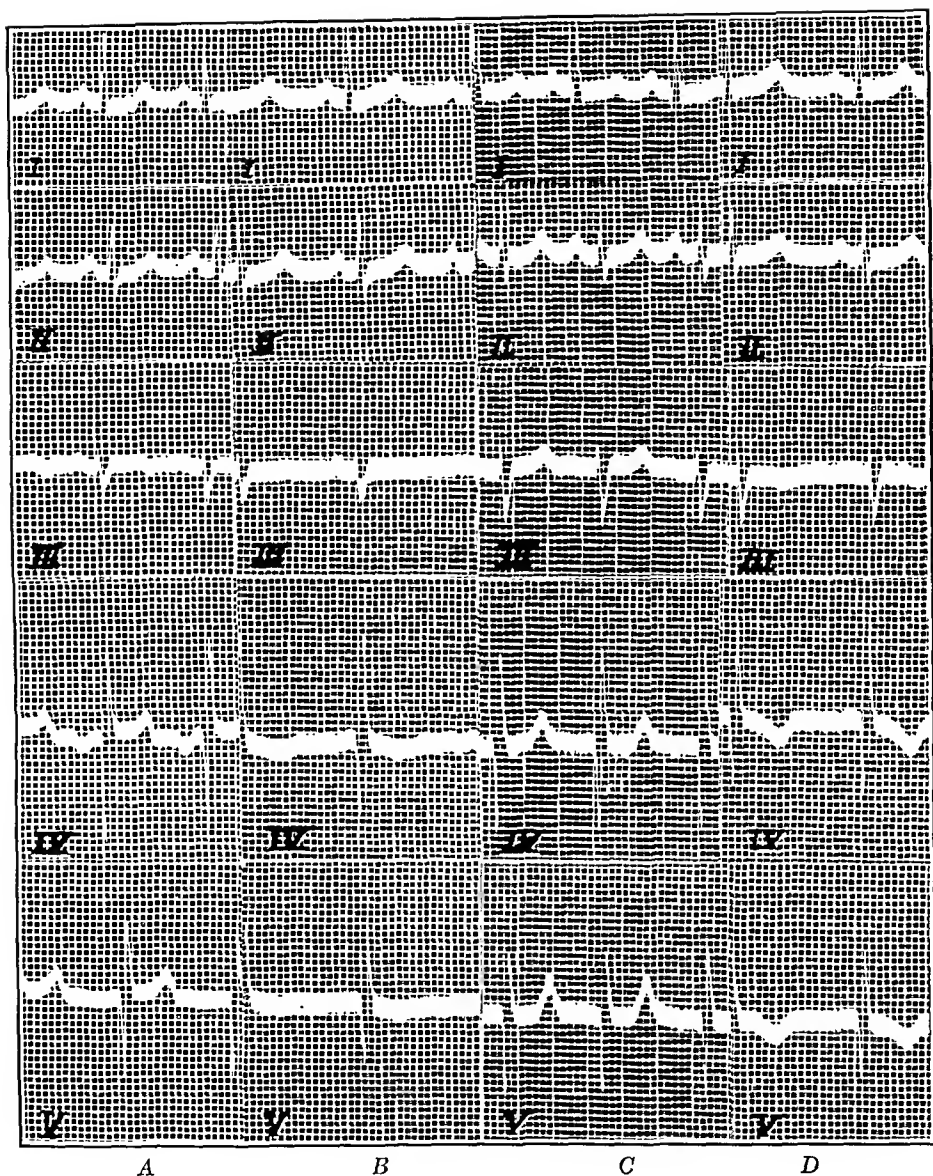


FIG. 2.—Electrocardiograms: (A) Before and after thyroideetomy. The only definite abnormality is the upright (pathologic) *T* waves in the precordial leads (IV and V). (B) Ten months after operation; at this time there was evidence suggestive of hypothyroidism. Note the flattening of the *T* waves in the precordial leads. (C) Fifteen months after operation; the attacks had recurred. The *T* waves in the precordial leads are again upright (pathologic). (D) Twenty-two months after operation and 4 months after last attack. The *T* waves in the precordial leads are inverted (normal). The precordial leads in all instances were taken with the right arm electrode at the fluoroscopic apex of the heart.

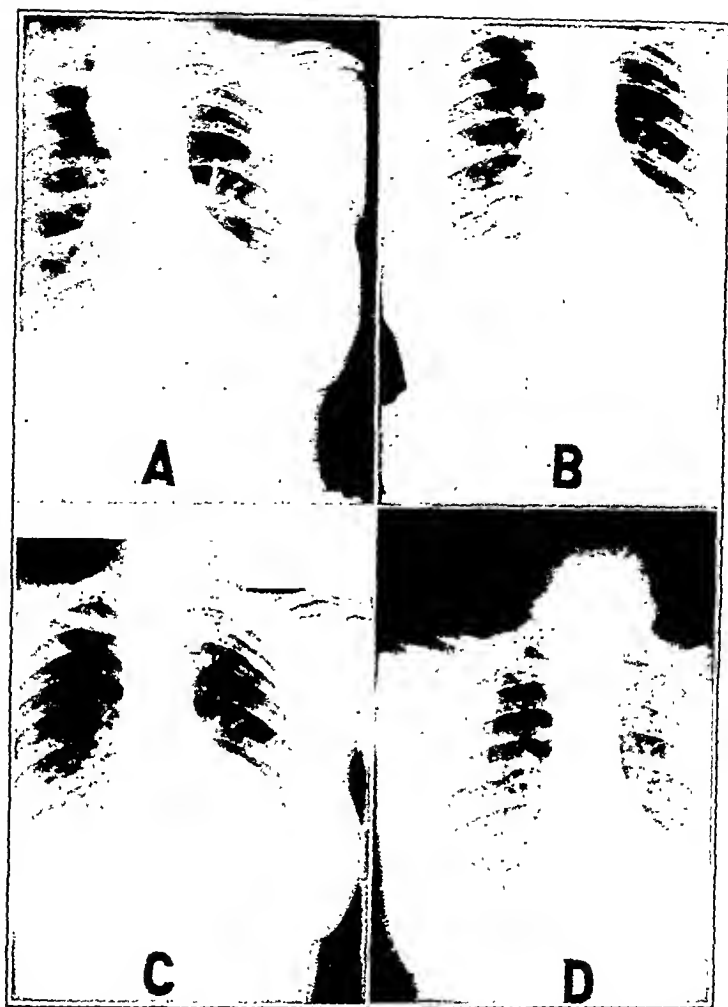


FIG. 3.—Roentgenographic appearance of the chest before and after thyroidectomy: (A) Before operation; note mediastinal mass, displacement of trachea of the left, and right scolirosis of cervical spine. (B) Two weeks after operation; mediastinal mass has disappeared but mediastinal shadow somewhat wide and dense; scolirosis and tracheal deviation still present. (C) Four weeks after operation; appearance essentially the same as B. (D) Twenty-one months after operation; mediastinum now seems normal. Scolirosis and tracheal deviation have now disappeared.

normal size, shape and position. The electrocardiogram showed upright (pathologic) *T* waves in the precordial leads; the limb leads were essentially normal (Fig. 2, A.)

She was admitted to the Medical Division of this hospital on November 16, 1935. Roentgen ray of the chest (Fig. 3) revealed the following: "The trachea is deviated considerably to the left by a substernal mass which is in the right upper thoracic region. The esophagus was also deviated to the left side. On swallowing, the mass went up into the neck and there was nothing to suggest an aneurysm of the innominate artery. The lung fields were clear. Diagnosis: Substernal extension of the thyroid on the right side producing tracheal deviation." Repeated electrocardiograms showed upright (pathologic) *T* waves in the precordial leads; the limb leads were essentially normal. Her basal metabolic rate was -9% . The blood count was normal. The blood urea nitrogen was 14 mg., sugar 90 mg. and cholesterol 250 mg. %. The urine was normal. Her blood Wassermann test was negative.

Attacks of pain occurred during the night but were not as frequent or severe as those experienced at home. All were relieved by nitroglycerin. It was decided to try the effects of Roentgen ray therapy and iodides, although no great change was anticipated if the mass were substernal thyroid. On December 5, 1935, Roentgen ray therapy was begun. Following each treatment, the seizures were more frequent and of increased intensity. After 5 daily treatments, during which a total of 1050 R was given, Roentgen ray of the chest showed no diminution in the size of the mass, although the roentgenologist considered the amount of treatment insufficient. Ten minims daily of a saturated solution of potassium iodide was given from November 28 until December 24, without apparent effect. The patient, refusing operation, left the hospital December 24, 1935.

The patient later consented to operation, performed January 22, 1936, by Dr. B. Lipshutz. The thyroid was found to be for the most part beneath the sternum, occupying the upper mediastinum, chiefly on the right side and adherent to the surrounding structures. The exact relation of the thyroid mass to the aorta could not be determined at the time of operation, although the Roentgen ray suggested a close approximation between them. With great difficulty, the gland was freed by finger dissection and a subtotal thyroidectomy performed. The dead space left in the upper mediastinum was filled with narrow gauze packing. The portion of the gland removed weighed 80 gm. *Histologic examination*, by Dr. David Meranze, showed two distinct pictures: areas of essentially normal thyroid, and areas showing acini greatly distended and distorted with faintly staining colloid substance. In the colloid areas the acini varied greatly in size, some apparently having fused. Their lining cells were extremely flattened and the contained colloid stained palely. Some acini were hemorrhagic and some were replaced entirely with hyaline material showing acicular spaces and lipid-filled cells.

Except for a cough, convalescence was uneventful and the patient was discharged from the hospital on February 4, 1936. The basal metabolic rate on February 4, 1936, was $+15\%$ and a Roentgen ray of the chest on the same day showed the absence of the previously reported supracardiac mass; the trachea continued somewhat compressed and displaced to the left, although less than before operation. The mediastinal shadow was still somewhat widened and abnormally dense. An electrocardiogram was not done.

When seen again, February 19, 1936, she reported several attacks of moderate pain of short duration. The electrocardiogram was essentially the same as before operation. On October 17, 1936, she complained of marked shortness of breath and sluggishness. The attacks, however, had

become increasingly infrequent. She had gained 36 pounds in weight since operation. The electrocardiogram (Fig. 2, *B*) showed flat *T* waves in the precordial leads. Her basal metabolic rate was -5% and blood cholesterol was 284 mg.%. She was placed on $\frac{3}{4}$ grain of thyroid substance (Armour) daily and on November 14, 1936, reported that she felt much better in general and that the attacks had been very infrequent and not severe. She had lost $5\frac{1}{2}$ pounds in weight. In the middle of December, 1936, she stopped taking thyroid. She was comparatively free of symptoms until February 1, 1937, when she developed an acute bronchitis which was accompanied by a sense of thoracic pressure but no pain. On April 28, 1937, she had a recurrence of the attacks. (Fig. 2, *C* shows the electrocardiogram on that day.) She was placed on $1\frac{1}{2}$ grains of thyroid substance daily which she took for 2 weeks. On October 12, 1937, she reported that she had not had any attacks except for a minor one in June. The electrocardiogram (Fig. 2, *D*) on that day showed inverted (normal) *T* waves in the precordial leads for the first time since she came under observation. (Fig. 3, *D* shows the Roentgen ray of the chest taken the same day.) Her basal metabolic rate on October 18, 1937, was $+5\%$ and the blood cholesterol was 403 mg.%. She was last seen on May 28, 1938, when she reported that she had had no further attacks since the slight one in June (about $11\frac{1}{2}$ months) and was feeling well in general.

Comment. Several features require comment. First, although relieved by nitroglycerin, the attacks of pain were nocturnal, and were not precipitated by exercise; indeed, at times exertion brought relief. Second, removal of the substernal goiter was not followed by immediate disappearance of the attacks; they continued to recur, though at infrequent intervals, for about 17 months after operation. Third, a scoliosis of the cervical spine to the right is apparent in the Roentgen rays taken before operation. This, together with the tracheal deviation, persisted for at least 1 month after operation. Some increase in width and density of the upper mediastinal shadow was also noted for the same length of time. All these findings had disappeared in the film made 21 months after operation, when the attacks had ceased. Fourth, the hypercholesteremia suggested some thyroid deficiency before operation (although the basal metabolic rate was not in conformity with this), and the picture was even more suggestive of hypothyroidism 9 months after operation. Finally, the electrocardiographic changes might have been associated with the goiter regardless of its location, as it has been shown that "non-toxic" goiter may be associated with a variety of electrocardiographic abnormalities (in limb leads at least) and that they may disappear at varying intervals after the removal of such goiters.⁴

Discussion. Several possible explanations for the relief following thyroidectomy may be considered.

1. A state of myxedema comparable to that produced by total thyroidectomy might have been produced. This is supported by the patient's appearance and the hypercholesteremia 9 months after operation. It is contradicted, however, by the basal metabolic rate and by her present appearance.

2. On the contrary, the coronary circulation might have improved following the removal of a mass of non-functioning thyroid tissue, a state of thyroid insufficiency having been thereby corrected. This possibility is eliminated by the marked hypercholesteremia found in October, 1937. Furthermore, the original attacks of pain were not of the type usually seen in persons with coronary artery disease.

3. Afferent nerve pathways contained in the vagus branches, the superficial or deep cardiac plexuses, a plexus in the upper posterior mediastinum,³ the superior or middle cardiac nerves, or ramifications thereof, may have been interrupted by the operation. Weinstein and Hoff⁵ have confirmed the intimate relationship between the superior and middle cardiac nerves and the sympathetic innervation of the thyroid. Subtotal thyroidectomy could thus have easily interrupted sensory impulses traveling through the superior or middle cardiac nerves.

4. Part of the intrathoracic thyroid mass may have produced the pain by pressure upon the periaortic part of the superficial cardiac plexus, and relief of this pressure by the operation may have relieved the pain. Both this and the preceding hypothesis, however, leave the electrocardiographic changes and the postoperative recurrences of pain unexplained.

5. The possibilities that the entire symptom complex may have been functional, or that the subsidence of the attacks bore no relation to the thyroidectomy, seem too remote to require discussion. It would appear that no entirely satisfactory explanation can be offered of the mechanism whereby relief of the pain in this case followed removal of the intrathoracic goiter. The persistence of the cervical scoliosis and tracheal deviation for at least 1 month after operation suggests the possibility of some residual exudate or inflammatory process in the bed of the mediastinal goiter, which might have been a factor in the postoperative recurrences of pain. The tracheal deviation may have played a part in the production of the attacks,² although dyspnea was not a symptom. From Bisgard's¹ report and our own experience, it seems justifiable to conclude that intrathoracic goiter, without the usual phenomena of hyperthyroidism, may be associated with typical angina pectoris or anginoid chest pain, and that relief may follow removal of the goiter.

Summary. The case is reported of a 45-year-old woman who suffered repeated severe attacks of thoracic and shoulder pain, who also presented electrocardiographic abnormalities, hypercholesteremia, and a large intrathoracic goiter in proximity to the aortic arch. Subtotal thyroidectomy was followed by marked reduction in the frequency and severity of the attacks, and eventually by their disappearance (for 11½ months up to the time of writing) and by the return of the electrocardiogram to normal.

Since the above was written attention has been called (Reid, W. D., *J. Am. Med. Assn.*, 110, 1724, 1938) to thoracic pain following compression of the brachial plexus by cervical rib or the scalenus anticus muscle, and a case cited in which such pain disappeared after correction of a left scoliosis. This suggests another possible explanation for the events in our case, *i. e.*, the goiter may have given rise to the right cervical scoliosis which in turn may have caused tension of the left scalenus anticus with brachial plexus compression, the syndrome being terminated by removal of the goiter and subsequent disappearance of the scoliosis. This would not, however, explain the electrocardiographic changes (see Fig. 3).

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ISOLATED CALCIFIED AORTIC STENOSIS.

WITH PARTICULAR REFERENCE TO ITS ETIOLOGY AND DIFFERENTIAL DIAGNOSIS.

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ALTHOUGH calcification of the aortic valve has received considerable attention during the past few years, its importance clinically is not generally appreciated. The early literature contains a few references to this lesion. As far back as 1672 Rayger³ described an autopsy in which there was "osseous fusion of the aortic cusps." In 1706, Cowper¹⁰ described a case with "petrification of the stenosed semilunar valves of the left ventricle." However, the first extensive study of this lesion was made by Mönckeberg in 1904.¹⁵ Interest in this particular condition has been revived recently by the pathologic studies of Margolis, Ziellessen and Barnes¹² and by Christian⁶ who accurately described the clinical picture. Sosman and Wosika¹⁶ outlined the roentgenologic technique for demonstration of calcified valves and reported 12 cases diagnosed during life. Willius and Camp¹⁸ discussed 15 cases diagnosed during life. Though Blackford, Bryan and Hollar¹ could find less than 50 cases of calcification of the aortic valve in the literature diagnosed during life, autopsy studies indicate that this lesion is not uncommon. Clawson⁷ found that in 253 deaths from lesions of cardiac valves, the aortic valve was calcified in 93. White and McGinn¹¹ state that 1.8% of routine autopsies and 2.3% of cardio-vascular cases show this lesion.

Clawson, Noble and Lufkin⁹ found that the aortic valve was involved in 54% of their total number of healed valve deformities.

Material. This study is based upon autopsy protocols of 9123 consecutive postmortem cases from three hospitals in Saint Louis (City Hospital No. 1, Jewish and Barnes) and 13,000 autopsies at Johns Hopkins Hospital;* a total of 22,123 autopsies. We were primarily interested in those cases showing pure aortic stenosis without involvement of other valves or chordæ tendineæ that would obviously suggest rheumatic fever as the etiologic agent. There were 72 such cases in this series. Only those cases showing at least a moderate degree of aortic stenosis were included in this study. A large number of cases with isolated sclerotic plaques on the aortic valve leaflets were not included, since no apparent stenosis was present. In 19 of the 72 cases, there was a co-existing arteriosclerotic involvement of the mitral valve, with marked calcification chiefly at the base of the valve. In none of these 19 cases was there any evidence of rheumatic involvement of the mitral valve.

In the 13,000 autopsies at Johns Hopkins Hospital there was a total of 89 recorded cases of aortic stenosis; occurring as an isolated aortic lesion in 24 and with combined involvement of other valves or chordæ tendineæ in 65. Those cases in which rheumatic fever was an etiologic agent almost without exception showed some involvement of the mitral valve. Among the rheumatic fever cases only 1 lived to be over 40. His death at the age of 43 raised the average age of death in this group from 22 to 24.

Analysis of the combined autopsy records, clinical histories and available gross and microscopic specimens of the cases of isolated aortic stenosis gave the following results.

Incidence. Seventy-two cases in 22,123 routine autopsies (0.32%).

Sex. Sixty-five (90%) of the 72 cases were males.

Age. The average age of the group was 60.5 years; 8 cases were under 50, 10 under 40. The youngest patient in this group was 32 years of age and the oldest 93.

Rheumatic History. Only 3 cases gave a definite history of acute rheumatic fever. One of these, who died at the age of 39, gave a history of acute rheumatic fever at ages of 23 and 25. At autopsy, the aortic valve showed moderate calcification, while the mitral valve was free of involvement. Another patient, who had acute rheumatic fever at 16 years and died at 34, at autopsy showed a thickened and fused aortic valve with minute fresh vegetations at the edges, some of which were calcified. It is felt that the history of rheumatic fever is unreliable—whether taken from hospital records or obtained from the patient. Previous attacks are often overlooked and may have been unrecognized. However, it is obvious that a positive rheumatic history in cases of isolated calcareous aortic stenosis is extremely uncommon.

Syphilis. Three cases had positive serologic tests, but there was no evidence recorded of luetic aortitis, grossly or microscopically.

Blood Pressure. In the 48 Saint Louis cases with records of blood pressure the average systolic pressure was 140, diastolic 67. The systolic pressure was over 160 in 9 cases and under 100 in 6; 5 patients had diastolic pressures below 60. The average pulse pressure of the group was 73. Six had a pulse pressure over 100. These figures show that approximately 87% of aortic stenosis cases will have a normal or decreased pulse pressure.

* It so happens that the first recorded autopsy at the Johns Hopkins Hospital was on a case of aortic stenosis combined with a vegetative and ulcerative endocarditis in a man, 68 years of age. The bacterial nature of the acute lesion was of course not studied. The upper portions of the valve leaflets are described as thickened and indurated.

In the Saint Louis series of 9123 cases there were 104 cases of luetic aortitis (an incidence of 1%). Four cases died so soon after admission to the hospital that no tests could be made. Of the remaining 100 cases, 93 had positive serologic tests; 6 were negative. In 1 case the blood Kahn and Wassermann tests were negative, while the spinal fluid Wassermann was positive. A microscopic diagnosis of luetic aortitis was made in each case. Several cases, previously diagnosed as luetic aortitis with negative serologic tests, were found to be purely arteriosclerotic on closer examination of the sections and were excluded. This indicates a higher incidence of positive blood tests in luetic aortitis than is generally reported. While definite cases of luetic aortitis with negative tests do occur, the diagnosis of luetic aortitis in the presence of a negative blood Kahn and Wassermann must be made with extreme caution, especially if it remains negative following a provocative test.

Clinical Course. The clinical picture of calcification of the aortic valve has been accurately described by Christian⁶ and more recently by Willius and Camp.¹⁸ The typical case is that of a male over 50 years, with the usual history of cardiac decompensation, a to and fro murmur or absent second sound with a thrill over the aortic area, a normal or decreased pulse pressure and a negative blood serology. Of course, some cases do not entirely fit this picture. There may be few symptoms referable to the heart and the stenosis is usually of long duration and marked in degree before signs of heart failure appear. In the presence of hypertension or a marked aortic stenosis with retraction of the cusps, the pulse pressure is increased. Although most of these cases terminate with the usual course of cardiac failure, death may occur very suddenly as described by Marvin and Sullivan.¹⁴ Boas² stresses the relationship of angina pectoris, heart block and aortic stenosis.

The physical findings can be clearly explained by the pathologic process. The signs are usually those of a stenosis with slight aortic insufficiency, in contrast to the free regurgitation and no stenosis of luetic involvement of the aortic valve. The calcification in aortic stenosis affects the valve leaflets and the base of the valve, but very rarely extends on to the aortic wall, so that there is no dilatation of the aortic ring. Usually the aortic wall in the proximity of the valve is remarkably free from atheroma. In syphilis, the essential lesion is a destruction of the media of the aortic wall and as it progresses toward the aortic ring produces dilatation and consequent signs of a free regurgitation. There is no impediment to the flow of blood in a luetic aortitis.

Case Reports. Some of the difficulties encountered in diagnosis are illustrated in the following cases:

CASE 1.—W. D., a white male, aged 53, entered the hospital irrational and in a critical condition. A history of antiluetic treatment for the past 4 years was obtained from his wife. His record showed a negative Wassermann and a 2+ Kahn test at the onset of antiluetic treatment. He was treated as a case of latent lues with bismuth and mixed treatment. Serologic examinations during the next 4 years were all negative and 2 spinal punctures were negative. On admission, the heart was enlarged; the

rhythm regular. There was a loud harsh systolic murmur heard over the aortic area. The aortic second sound could not be heard. There was a soft systolic murmur at the apex. No thrill was felt. There was no widening of the supracardiac dullness on percussion. The blood pressure was 95/72. There was no edema. The remainder of the examination was negative except for generalized arteriosclerosis. The Kahn test was negative. W.B.C. 12,500; R.B.C. 4,800,000; Hb. 80; urine showed moderate amount of albumin with an occasional cast; NPN 30; sugar 92; spinal fluid was normal.

The *clinical diagnosis* was syphilis of the central nervous system and aortic stenosis or luetic aortitis. The patient expired 4 days later.

At *autopsy* there was a marked calcified stenosis of the aortic valve. The other valves were normal. There was a generalized arteriosclerosis. There was no evidence of luetic aortitis.

The picture that this patient presented was typical of a calcareous aortic stenosis.

CASE 2.—K. G., a white female, aged 54, entered the hospital complaining of generalized weakness, dyspnea, and precordial pain. She had been in the hospital 1 year previously and had been diagnosed as a case of luetic aortitis. The essential physical findings were: irregular pupils which reacted sluggishly to light; moist râles in bases of the lungs and slight peripheral edema; the heart was enlarged. A to and fro murmur was heard over the aortic area and a soft systolic murmur at the apex. The blood pressure was 200/60 and a generalized arteriosclerosis was present. The Kahn and Wassermann reactions were 4+ positive. NPN 19; sugar 77; W.B.C. 7200; R.B.C. 3,200,000; Hb. 70%; urine was normal. The electrocardiogram showed evidence of myocardial lesions or digitalis effect with ventricular extrasystoles.

The *clinical diagnosis* was luetic aortitis with aortic regurgitation. She was digitalized with slight temporary improvement and expired 3 weeks later.

At *autopsy* there was no evidence of a luetic aortitis, either grossly or microscopically. The aortic valve showed marked calcification involving the entire aortic ring. The other valves were remarkably free from involvement. There was a generalized arteriosclerosis.

CASE 3.—A. F., a white male, aged 49, entered the hospital complaining of dyspnea, precordial pain and edema of 3 months' duration. On examination, the heart was enlarged and there was a loud harsh systolic murmur and a soft diastolic murmur heard over the aortic area and a soft systolic murmur over the mitral area. The blood pressure was 180/65. There was a peripheral edema. The Kahn reaction was negative. Urine showed moderate albumin. W.B.C. 10,600; R.B.C. 4,700,000; Hb. 80; NPN 31; sugar 92. The electrocardiogram showed auricular fibrillation and ventricular extrasystoles.

The *clinical diagnosis* was luetic heart disease with aortic regurgitation and decompensation.

At *autopsy* there was no evidence of a luetic aortitis, either grossly or microscopically. The aortic valve showed marked calcification and stenosis. There was also a generalized arteriosclerosis.

Etiology. There has been considerable controversy regarding the etiology of isolated aortic stenosis and the question is still far from settled. Various workers believe that it is the result of an inflammatory involvement of the valve, such as rheumatic fever or bacterial endocarditis; others maintain that the lesion is purely non-inflammatory—the result of a degenerative metabolic process.

Others believe that either or both causes may be active, while still others hold that the etiology of the lesion is entirely unknown. Mönckeberg,¹⁵ in 1904, studying aortic valves in which there was extensive calcification, decided that the process in the cusps was the same as that found in the intima of the aorta in senile arteriosclerosis. Margolis, Ziellessen and Barnes¹² and Clawson, Bell and Hartzell⁸ believe that some of these cases represent a non-inflammatory degenerative process. Clawson,⁷ in an analysis of Mönckeberg's work, stated that there was no support for the metabolic theory of the structural changes in these valves and he thought that an infectious basis was more probable. Christian⁶ and Clawson, Noble and Lufkin⁹ believe that rheumatic fever is the cause. Cabot⁵ suggests that the lesion may follow bacterial endocarditis. Mallory¹³ believes that this lesion is rarely rheumatic in origin.

The question of etiology is obviously difficult: for instance, most of the cases as seen at autopsy present the final stages of a process without any clue as to its origin. The variance of opinion among experienced authors about this question would suggest that no one factor is the sole etiologic agent for the entire group. There are good arguments for and against each of the various theories proposed.

In *acute rheumatic fever* the involved valve becomes swollen and thickened and small bead-like vegetations form along the line of contact of the valve. Boyd⁴ stresses that the essential valvular lesion in acute rheumatic fever is an inflammation of the entire valve, a valvulitis, and that the vegetations are to be regarded as merely incidental: there are Aschoff bodies and an increased number of fibroblasts; the chordæ tendineæ and wall of the auricles are often affected. In the healing stages, fibrous tissue forms to produce dense scar tissue. In later years, lime salts may be deposited to produce calcification or even true bone. Boyd⁴ also states that in every case of rheumatic carditis, the mitral valve is injured.

The main lesion in the healed rheumatic valve is fibrosis. If there is a co-existing involvement of the mitral valve with thickening and fibrosis, or involvement of the chordæ tendineæ, the etiology is rheumatic. In an isolated aortic lesion, with a normal mitral valve, fibrosis and thickening of the edges of the cusps, indicate that the etiology is probably rheumatic. On the other hand, if the valve shows a sclerotic base with calcified nodules scattered over the valve and the remainder of it is thin and not fibrosed, the lesion is probably arteriosclerotic. White¹⁷ states that when the entire valve is calcified with retraction and marked stenosis, Mönckeberg's sclerosis alone is not to blame, but rather a combination of the old infectious process and superimposed calcification.

The occurrence of a calcareous lesion in the aortic valve alone, without involvement of the other valves is important but not conclusive evidence against a rheumatic etiology, because the proven rheumatic aortic lesion usually has associated mitral damage.

Further evidence against a rheumatic etiology is the large incidence among males and the advanced age at death (90% males and average age of 60 years in our series). White¹⁷ states that rheumatic fever affects females more commonly than males in the ratio of about 5 to 4 or 4 to 3.

Aortic stenosis of rheumatic origin, however, becomes calcified relatively early, and only a few cases are seen at autopsy with a pure fibrotic lesion. The stenosed rheumatic mitral valve consists of a thickened fibrous hyalinized mass and calcification is unusual except in very old individuals. It seems strange that the course of this lesion in the two valves in such close proximity is so different. Another interesting observation is that in most of the cases of calcified aortic stenosis the proximal portion of the aorta is relatively free of atheroma.

In valvular *arteriosclerosis* of the atherosclerotic type, subendothelial fatty deposits and fibrosis precede deposition of lime salts. The process can affect any portion of the valve, but is more common at the base of the valve. The earliest example of this process was seen in a recent autopsy, in which there was a small lesion on one of the aortic cusps. The mitral valve was entirely normal as were the other two aortic cusps. The lesion was located near the base of the valve, about 5 mm. in diameter on the aortic side, was well localized and showed early calcification. The remainder of the valve was smooth, thin and entirely normal. The aorta showed marked *arteriosclerosis*. This lesion certainly appeared degenerative and it is highly improbable that it could be the result of an inflammatory process. Progression of the lesion and the formation of similar areas on the other aortic cusps would in time undoubtedly produce a typical calcified aortic stenosis. While there is usually an accompanying *arteriosclerosis* of the aorta, this is by no means constant.

There seems to be relatively little in the literature regarding the rare *arteriosclerotic* involvement of the mitral valve. It seems fairly definite that this process affects primarily the base of the valve with degeneration and later calcareous deposits. This produces a calcified bar around the base of the valve, leaving its edges remarkably free. It is unusual for the process to become so extensive that the entire valve leaflets of the mitral valve are involved by these calcareous deposits, except in very old patients. The same process usually extends on to the aortic valve which lies in close proximity.

An uncomplicated *luetic* aortic valvulitis is usually accompanied by *luetic* aortitis and rarely calcifies. However, neither of these criteria always maintains.

So it would appear that no one etiologic factor is responsible for all cases of calcification of the aortic valves. Sometimes the lesion is inflammatory, sometimes degenerative and in still other cases both processes are probably present. Careful examination of the affected

valve and the appearance of the other valves, particularly the mitral, will often indicate the probable etiology. In cases of isolated aortic stenosis, arteriosclerosis is usually the cause. However, it is often impossible to determine the etiology in a far-advanced aortic stenosis.

Diagnosis. The clinical diagnosis of calcareous aortic stenosis should not be difficult if the condition is kept in mind. The various characteristics of the clinical course have been discussed, which are primarily the signs of an aortic stenosis with slight regurgitation in an old person with a negative serology. A valuable aid in the diagnosis of this lesion is the Roentgen ray, according to the technique described by Sosman and Wosika.¹⁶ They were able to diagnose a large percentage of these cases by the use of the fluoroscope and Roentgen ray films. This method of examination has been of definite value, if there is a fair degree of calcification present. Fluoroscopic examination, showing the characteristic movements of the calcified valve with each heart beat, is more reliable than the Roentgen ray films. It must be remembered that a special technique is necessary to visualize these valves on a film, since the ordinary routine Roentgen ray of the heart will not show calcification within the heart.

Luetic aortitis frequently enters into the differential diagnosis. If the classical signs of both lesions are carefully considered, the diagnosis should not be difficult. However, in some cases (such as those presented) the diagnosis may be very difficult, particularly if serologic tests are positive and the pulse pressure is elevated. At present there is a general tendency to diagnose luetic aortitis rather freely, regardless of the blood serologic tests. The diagnosis of a luetic aortitis with negative serologic tests should be made with great caution, for it entails a tedious and expensive treatment and offers an entirely different prognosis. If there are signs of an aortic regurgitation and the blood serologic tests are negative, the possibility of an aortic stenosis must be carefully considered. The frequent teaching that a to and fro murmur over the aortic area, in the absence of mitral involvement, is invariably syphilitic is certainly not true.

Conclusions. 1. Isolated calcareous aortic stenosis has a characteristic clinical and pathologic picture.

2. A study of 72 cases of isolated aortic stenosis found in 22,123 consecutive postmortem examinations is presented.

3. There were 104 cases of luetic aortitis in 9123 autopsies in the Saint Louis group.

4. The etiology of calcareous aortic stenosis seems impossible to decide with certainty. It is believed that in isolated aortic valve involvement, arteriosclerosis is the usual cause, but it can also result from an inflammatory process and in some cases from both.

5. The diagnosis can be made in most cases if the clinical characteristics and the possibility of a calcareous aortic lesion are kept in mind. The fluoroscopic and Roentgen ray methods of examina-

tion of the heart valves are of definite value and should be more commonly utilized.

We are grateful to Dr. W. G. MacCallum of Johns Hopkins University, Dr. S. H. Gray of St. Louis City Hospital and Jewish Hospital, Dr. H. A. McCordock of Barnes Hospital and Dr. P. A. Wheeler of St. Louis City Hospital for permission to use the data on the cases from their respective pathological departments.

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VARIETIES OF SINGLE CORONARY ARTERY IN MAN, OCCURRING AS ISOLATED CARDIAC ANOMALIES.

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CONGENITAL absence of one or other coronary artery appears to be a very rare anomaly in man. Especially is this so when it satisfies Hyrtl's postulate that one artery really supplies the whole heart, and the anomaly is not merely a matter of a common aortic orifice of the two arteries or an unusual origin of one of the other artery (*i. e.*, a misplaced anlage). Slightly misplaced or accessory coronary orifices are not uncommon (see Richter¹⁴). One of us⁹ has already reported a case where, associated with idiopathic cardiac hypertrophy (von Gierke's disease?), the left coronary artery arose from the pulmonary artery without noticeable damage to the left ventricle. The variability of coronary artery distribution is well shown in the article by Ehrlich, de la Chapelle and Cohn.⁴

We wish to record 2 cases of congenital absence of a coronary artery, both incidental findings at autopsy, in one of which the left

coronary artery and its branches supply the whole heart, while in the other a large right coronary early in its course gives off a branch which passes behind the aorta, past the usual site of origin of a left coronary, and is distributed to part of the left ventricle. As study of the literature indicates that these 2 cases are characteristic of the two chief varieties of absence of a coronary artery in man, a classification has been attempted.

CASE 1.—(P. G. H. Aut. 34,791.) A small, obese woman, aged 44, died of a pulmonary embolism. Previous to her last illness there were no signs of cardiac weakness observed. No history of cardiac anomalies in the family was elicited. *Autopsy* (Dr. W. E. Ehrich), in addition to the pulmonary embolism, revealed an enlarged heart (400 gm.) and a chronically thickened mitral valve.

*Coronary Artery System.** The right coronary artery is completely absent. There is no sign of an orifice in the pulmonary or high in the aorta or in the right anterior sinus of Valsalva. A large left coronary, showing a moderate degree of sclerosis, arises from its normal site in the left sinus of Valsalva. Its circumflex portion follows a normal course in the coronary sulcus, but continues all the way around the right ventricle to a point within 1.5 cm. of the aorta, where it divides into small terminal branches. It gives off the normal anterior descending branch and one in the posterior interventricular septum, similar to that normally arising in this position from the right coronary. The anterior descending can be opened to the very apex where it is lost in fat (*i. e.*, somewhat further than normal) (Fig. 1). No abnormal branches are found. Sections from the right ventricle show normal musculature, with no signs of degenerative or inflammatory change. There is some penetration of pericardial fat between the myocardial bundles.

CASE 2.—(P. G. H. Aut. 35,147.) An emaciated negress, aged 35, died of carcinoma of the uterus with widespread metastases. There were no clinical indications of a deficient circulation and no history of cardiac anomaly in the family was obtained. *Autopsy* (Dr. W. E. Ehrich), in addition to the carcinomatosis, revealed absence of the left coronary artery, otherwise a normal heart (285 gm.), a practically normal aorta, and thrombosis of the left iliac vein.

Coronary Artery System. A very large right coronary artery (1 cm. in circumference) arises from the right anterior sinus of Valsalva and no vestige of a left coronary artery can be found. As the right coronary is traced, it is found to give off—2 cm. from its origin—a branch (4 to 5 mm. in circumference) which courses posterior to the aorta and between it and the left auricular appendage. It can be traced to the base of the left ventricle, where it gives off branches that supply a major part of the left ventricle (and presumably, the left auricle). The right coronary artery also gives off a moderate-sized branch, 2 mm. from its orifice, which disappears into the septum, but does not reappear, as in Bochkalek's and Sanes' cases (to be mentioned later). These branches thus constitute a partial substitute for the missing left coronary. The main artery follows its normal course in the A-V groove, giving off several large branches (Fig. 1), and ending in several terminal twigs on the posterior surface of

* As both hearts here described were opened routinely, the anomalies being unexpected findings of the postmortem examination, injection preparations were not feasible. The anomalous arrangement and distribution, however, could be readily made out in each case by exploration with forceps and fine scissors.

the left ventricle, shortly after passing the interventricular septum. The branch that most closely corresponds to the posterior descending arises at the right border, passing horizontally across the posterior surface until it reaches a point above the interventricular septum, when it turns and

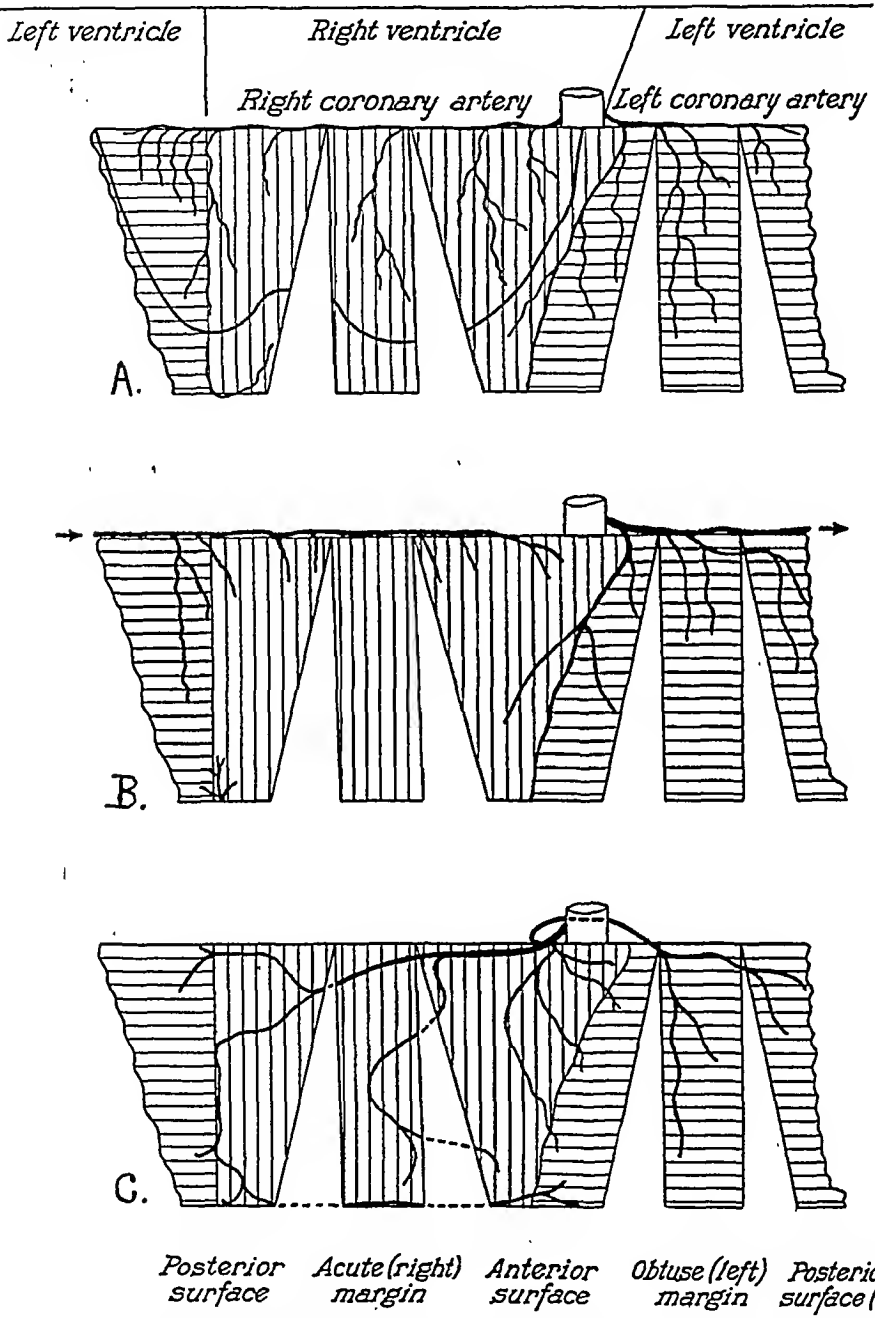


FIG. 1.—A, Diagram showing average distribution (after injection with barium-gelatin mixture) of the superficial coronary arterial system (from Ehrlich, de la Chapelle and Cohn). B, Distribution of left coronary and branches in Case 1 (absent right coronary artery). C, Distribution in Case 2 of right coronary and branches (absent left coronary artery). Note: The large septal branch arising close to the aortic orifice has not been drawn, as these diagrams represent the superficial only.

courses along the septum at least as far as the apex. Sections from various parts of the heart, including the base of the left ventricle, show some increase of fine periarterial fibrosis, equally throughout the heart.

Comment. These cases have been assembled with those found in the literature into three tables: Table 1, cases of absent right coronary artery, all of which comply with Hyrtl's concept; Table 2, cases of absent left coronary artery, where the left heart is supplied by one or two apparent branches of the right coronary; Table 3, miscellaneous unclassified cases. Our Case 1 appears to satisfy Hyrtl's postulate that one artery should supply the whole heart,

TABLE 1.—CASES OF ABSENCE OF RIGHT CORONARY ARTERY.*

Remaining artery supplies both sides of heart, with normal or almost normal distribution of branches (Hyrtl type).

Author.	Missing cor.	Age, (yrs.).	Sex.	Method of compensation.	Cause of death.	Wt. of heart (gm.).
Plaut (1922)	R.	37	M.	L. (left) cor. traverses entire cor. sulcus with a normal ant. desc. and large branches arising at R. (right) and L. borders of heart; a large branch from ant. desc. crosses R. V. to heart border; R. cor. is represented by small brownish dimple in aorta that is without functional significance	Endocarditis lenta.	
Petren (1930)	R.	33	M.	Half way down ant. surf. of heart, ant. desc. curves around R. V. and upward to post. furrow; L. circumflex continues well beyond post. furrow to within 1 cm. of aorta, giving branches to both vents. and ends in 2 small branches to R. A. and R. V.	Apoplexy	520
Kockel (1934-1935)	R.	39	F.	L. circumflex continues around to ant. surf. of R. V. with various branches to R. A. and R. V., as well as customary L. cor. branches	Pneumonia.	
Richter (Case 1) (1937)	R.	63	M.	L. cor. arises 2 cm. above sinus; its circumflex continues around R. V. to conus pul. with appropriate branches	Ca. of stomach, etc.	150
Krumbhaar and Ehrich (Case 1)	R.	44	F.	The circumflex branch of L. cor. continues around R. V. to within 1.5 cm. of the aorta; its branches correspond to those normally given off by both R. and L. arteries; no anomalous branches found	Chr. valvular disease; pulmonary embolism.	400

* In none of the cases listed in this and the succeeding table was myocardial weakness attributed to the anomalous arterial supply. Early reported cases, such as Thebesius' (1716), Otto's (1830), Hyrtl's (1841), are regarded as too indefinite to be tabulated.

without conspicuous anomalous branches. Here there is no question of a misplaced anlage, or of an anomalous vessel that might be regarded as an abortive right artery. The large branches that normally come from the right here arise from the left coronary. Thus it falls in the same group as Petren's,¹² Kockel's,⁸ Richter's first case and Plaut's¹³ (though here a small dimple apparently represented the anlage of the missing vessel). It is perhaps not a coincidence that in all of these cases it was the right coronary artery that was missing, though we know of no explanation for such a correlation.

The nature of the compensatory arrangement of the cases in Table 2 is debatable. In our Case 2, for example, although the



A

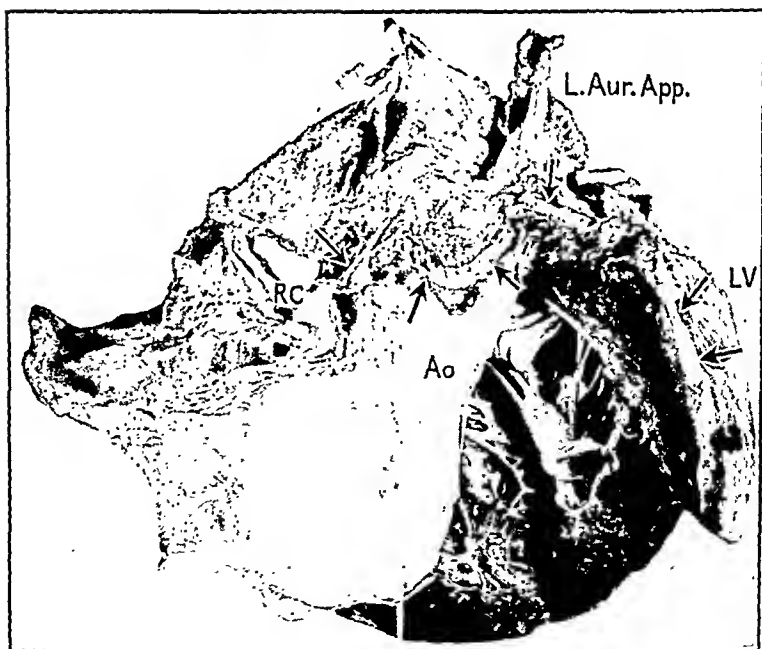


B

FIG. 2.—Case 1. A, Showing a large single orifice in the left sinus of Valsalva. B, A superoposterior view of the heart showing the opened single left coronary artery as still a large vessel on the posterior surface of the right ventricle.



A



B

FIG. 3.—Case 2. A, Showing a large single orifice in the right sinus of Valsalva (when the heart was opened in this case, the septal cut was made further to the right on the anterior wall than in Case 1). B, A superior view of the heart showing the opened anomalous branch (marked with arrows) arising from the right coronary, passing between the aorta and left auricular appendage to be distributed to the upper left ventricle.

anomalous branch that fed the basal part of the left ventricle, arose well down the right coronary and thus several centimeters from the normal site of origin of the left coronary, it eventually followed the course of a hypoplastic left coronary and *might* be regarded as a left coronary, arising from a badly misplaced anlage. To the writers it seems more probable that Case 2, like the others

TABLE 2.—CASES OF ABSENCE OF LEFT CORONARY ARTERY.*

The left side of the heart is supplied by 1 or 2 large, more or less abnormal, vessels that appear to be hypertrophied branches of the right coronary but suggest the possibility of misplaced anlage of origin.

Author.	Missing cor.	Age (yrs.).	Sex.	Method of compensation.	Cause of death.	Wt. of heart (gm.).
GROUP 1.— <i>Substitution by 2 Branches of Right Coronary: a Septal Branch, Behind Aorta, and One Passing</i>						
Bochdalek (1867)	L.	60	F.	R. cor. divides in 3 branches, the first of which follows normal course of R. cor.; the second, passing behind aorta, substitutes for L. cor; the third passes between aorta and pul. art. through sept., substituting for ant. desc.	Chr. mitral and aortic endocarditis	
Sanes (1937)	L.	3	M.	Large art. arising in R. sinus (a dimple adjacent) shortly divides into 3 branches: 1, an enlarged R.; 2, an anomalous L., passing between A. and L. A. to cor. sulcus, corresponding to a L. circumflex; 3, a branch sinking into the sept. between A. and pul. art. to appear on ant. surf. like ant. desc.	Acute glomerulonephritis	
Krumbhaar and Ehrich (Case 2)	L.	35	F.	Arising from large R. cor. (2 cm. from aorta), a large anomalous branch (4 to 5 mm. in diam.) passes behind aorta and between it and L. auric. appendage to feed upper half of L. V.; another large branch passes between aorta and pul. art. to V. sept.; the main art. continues in A-V groove past intervent. sept. post. where it ends in several small branches; it furnishes both ant. and post. desc. branches	Carcinomatosis	285
GROUP 2.— <i>Substitution by Septal Branch Only.</i>						
Gallavardin and Ravault (1925)	L.	45	F.	R. cor. divides almost at orifice into 2 equal branches, 1 acting as R., the other as L. cor., with circumflex and ant. desc. branches; the left branch, however, passes between aorta and pul. art.	Chr. mitral and aortic endocarditis	
Born (1933) (1 case)	L.	54	M.	Approx. nor. R. cor. goes in cor. sulcus to L. border of heart; large branch, starting near aortic orifice, goes between aorta and pul. art. into vent. sept. to reach ant. sulcus where it divides into an ant. desc. and a circumflex branch	...	750
Kintner (1931)	L.	65	M.	From a single orifice in R. sinus a large R. cor. pursues a normal course; an anomalous branch passes between aorta and pul. art. down and to L. reaching sept., where it curves ant. and just before reaching the surf. gives off branches corresponding to ant. desc. and L. circumflex	Pneumonia and renal insufficiency	

* The question as to whether these cases represent true absence of an artery or misplaced anlage is discussed in the text.

in Table 2, represents a true absence of the left coronary and that the substitute was a true branch of the right coronary, hypertrophied to meet the demand caused by the absent left coronary. Especially does this seem probable in the 3 cases of this group in which two separate branches of the right coronary substitute for the missing vessel. In any case, however, it is clear that none of the hearts in Tables 2 and 3 satisfies Hyrtl's postulate. For various reasons, these cases are difficult to evaluate. For instance, we have no definite way

of deciding whether a given anomalous vessel merely arises from a misplaced origin, or whether it is a branch developed to take the place of the missing vessel and distributed more or less in the same way. The dimple adjacent to the single coronary orifice in Sanes' case suggests that this, as in Plaut's case, represents a missing anlage and that the entire coronary system in these cases has arisen from one anlage. This phase of the subject need not be further elaborated here.

TABLE 3.—MISCELLANEOUS UNCLASSIFIED CASES OF ABSENT CORONARY ARTERY.

Author.	Missing cor.	Age (yrs.).	Sex.	Method of compensation.	Cause of death.	Wt. o heart (gm.).
Engelmann (1893)	R.	Large L. circumflex passes far onto post. surf. of R. V.; 1 cm. below beginning of normal ant. desc. a very large anomalous vessel passes obliquely over lower half of R. V. to divide in terminal branches on post. surf. of R. V.; a small vessel arises from L. cor. to pass between aorta and pul. art. to a point behind R. auric. appendage supplying post. R. V.	...	
Smith and Graber (1926)	L.	46	M.	The only cor. arising from aorta follows normal course of R. cor. to post. vent. sept.; here it divides into a larger desc. branch and a smaller branch which continued in A-V groove; post. desc. branch after reaching apex passed upward along ant. intervent. groove to anast. with a branch from first portion of main art.; the combination anastomosing also with a branch from post. desc.*	Coronary obstruction	930
Richter (Case 2) (1937)	R.	Adult	..	L. cor. divides into 3 branches: 1, ant. desc. which continues 5 cm. past the apex on post. wall; 2, a small L. circumflex, finishing behind L. auric. appendage; 3, a large branch, that goes over conus pul. to cor. furrow of R. V.; two of its branches supply post. surf. of R. and L. Vs.	...	370

* The anomalous arterial supply of the left ventricle in this case is apparently unique in the literature. Description is not sufficiently detailed to carry intrinsic proof of what appears to be an improbable explanation.

The cases of Bochdalek¹ and Sanes¹⁵ comes closest to our second case, in that both, having but one coronary orifice, present anomalous branches of the right coronary, one of which passes behind the aorta and then between it and the left auricle to the left ventricle; while another passes into the ventricular septum. In these cases, however, the septal branch was more important than in our case, reappearing after its passage through the septum on the surface of the ventricle, which ours did not.

In the cases of Born,² Kintner,⁷ and Gallavardin and Ravault,⁵ on the other hand, substitution is accomplished by one anomalous branch of the right coronary, which, either sinking into the septum (Born) or passing between aorta and pulmonary artery (the other 2), appears on the anterior surface to give rise to a left circumflex and an anterior descending artery. As to the question whether these cases should be regarded as examples of anomalous origin of the left coronary or of its true absence, the division of the main artery into right and left branches almost at the aorta would favor the former view; the markedly anomalous and differing courses, the latter view. Though Kintner and Sanes regarded their cases as representing an

anomalous left coronary, there was but one orifice and the distribution was anomalous. The descriptions clearly place both in our Table 2.

The cases of Engelmann,³ Smith and Graber,¹⁷ and Richter¹⁴ (Case 2) have been assembled in a miscellaneous group that resists classification. Such cases as those of Kugel,¹⁰ de Vries,¹⁸ Shapiro,¹⁶ Mönckeberg¹¹ and Walcher¹⁹ are not considered here, both because of inadequate description in some cases and because they all were associated with other grave cardiac anomalies. No other clear cases of absent coronary artery have been found by us in the literature.

The pathogenesis of these anomalies cannot yet be explained. Some authors have attributed the absence of one of the arteries to lack of the appropriate anlage, as the Plaut and Sanes dimples would suggest; others (with less probability) to closure of the vessel in question in fetal life. The possibility of the anomaly being due to a misplaced origin of one of the coronaries in some of the cases has already been mentioned.

Summary. 1. Two cases of absence of a coronary artery are reported, both incidental findings at autopsy, and apparently causing no damage to the myocardium.

2. In the first case, a large left coronary continued around the A-V groove, to the anterior surface of the right ventricle, giving off branches that corresponded to those normally given off by both arteries (Hyrtl type of absent coronary).

3. In the second case, a large right coronary artery supplied most of the heart with conventional branches. Near its origin, however, it gave off one large anomalous branch which passed behind the aorta to supply a good part of the left ventricle and another to the ventricular septum. The possibility must be considered that the former of these represents a true left coronary arising from a misplaced anlage, though the similar cases of Bochdalek and Sanes makes this very unlikely.

4. Other cases of absence of a coronary artery, or possibly misplaced anlage of origin, are tabulated, all but 3 of which fall into two groups corresponding to the types of the 2 cases reported here.

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THE ANEMIA OF ALCOHOL ADDICTS.

OBSERVATIONS AS TO THE RÔLE OF LIVER DISEASE, ACHLORHYDRIA, NUTRITIONAL FACTORS AND ALCOHOL ON ITS PRODUCTION.

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RECENT studies from this clinic on the polyneuritis of the alcohol addict^{3,8-10} have made us aware of the frequent occurrence of macrocytosis and macrocytic anemia in these patients. Spies and Chinn,¹² in a study of pellagrins, most of whom were alcohol addicts, found quantitative anemia in about two-thirds of their subjects. In 75% of these, the anemia was of the macrocytic hyperchromic variety. Several observers have called attention to the frequent occurrence of macrocytic anemia in subjects having cirrhosis of the liver; Wintrobe^{15b} reported the incidence to be about 40% in 44 subjects, while Rosenberg and Walters¹¹ reported macrocytosis in about 90% of their 48 patients, 31 of whom were known alcohol addicts. Macrocytic anemia, therefore, is frequently observed in 3 syndromes common in alcohol addicts: polyneuritis, pellagra and liver cirrhosis. As data are not available concerning quantitative measurements of the red blood cells in alcohol addicts, we are unable to determine whether the high incidence of macrocytosis is characteristic only of polyneuritis, pellagra and liver cirrhosis, or possibly of an underlying liver disease, or of alcohol addiction itself; or whether some other factor plays the decisive rôle. To decide this point, if possible, is the purpose of the present study.

The subjects in this study are 159 alcohol addicts admitted to the wards of the Psychiatric Division of Bellevue Hospital who presented evidence of polyneuritis (139), pellagra (40), "alcoholic" encephalopathy¹ (24), liver cirrhosis (30), and "alcoholic" stomatitis² (48), and were therefore transferred to the division's medical service. Many of the subjects presented two or more of these syndromes simultaneously. This group of 159 patients is hereafter, for convenience, referred to as the "complicated" group. Patients having surgical complications, acute infections, syphilis, or tuberculosis, are not included in this group. An additional group of 25 alcohol addicts who showed none of the above clinical pictures or other stigmata of alcohol addiction were selected for control observa-

tions. Each subject in this group had had two or more previous admissions within a year to the alcoholic wards. This latter group is hereafter, for convenience, referred to as the "uncomplicated" group.

During the first 3 to 5 days of hospitalization, while the blood studies and routine observations were carried out, all the patients received our ward basal diet.⁸ Following these observations, therapy was instituted. This report, however, deals only with the blood status as found during the preliminary period of observation.

Methods. In the first 61 subjects, Haden's⁴ constants, corrected for our laboratory, were determined. The corrected values were obtained by determinations in 20 apparently normal subjects. In the remaining 123 subjects Wintrobe's^{15a} methods were followed. In order to tabulate and average the size of the red cells, the maximum normal size of each method is designated as 100%. The size of the red blood cells is therefore reported in per cent of the maximum normal size.

Arbitrarily we have chosen the following values as normal:

Red blood cells: 5,000,000 = 100%.

Hemoglobin: 14.5 gm. per 100 cc. = 100%.

Color index: 0.85 to 1.15.

Volume index: 0.85 to 1.15 (1.15 = 100%).

Mean corpuscular volume: 75 to 95 cu. μ (95 cu. μ = 100%).

The anemia found is classified according to size and color index of the red cells. Following Wintrobe's^{15a} criteria and classification, our subjects showing anemia are divided into four groups: macrocytic, normocytic, simple microcytic, and microcytic hypochromic anemia.

Gastric analyses and liver function studies were performed by methods described in previous publications from this clinic.^{6,7}

TABLE 1.—QUANTITATIVE DATA ON THE RED BLOOD CELLS OF 184 ALCOHOL ADDICTS.

Group.	No. of subjects.	RBC in millions.			Hgb. in grams.			Color index.			Size of RBC in % of max. normal.		
		Mean.	Variation.		Mean.	Variation.		Mean.	Variation.		Mean.	Variation.	
			Min.	Max.		Min.	Max.		Min.	Max.		Min.	Max.
Uncomplicated	25	4.81	4.19	5.48	13.5	11.1	15.4	0.98	0.91	1.15	102	68	120
Complicated	159	3.80	1.64	5.95	12.1	4.7	18.2	1.11	0.70	1.48	101	61	175
No anemia	62	4.58	4.00	5.95	13.9	8.6	18.2	1.04	0.72	1.37	101	80	120
Anemia	97	3.19	1.64	3.97	10.5	4.7	14.6	1.15	0.70	1.48	101	61	175

Results. We have arbitrarily designated subjects having 4 million or more red cells as not anemic, and all subjects having less than this number as having anemia. On this basis none of the "uncomplicated" subjects, and 61% of the "complicated" subjects show anemia. In Table 1 we have tabulated in the two major

groups the average, as well as the minimum and maximum, red blood cell count, grams of hemoglobin, color index, and size of the red cells; the "complicated" group was further subdivided into those with and without anemia. The average size of the red cells in the two major groups is practically identical, corresponding to about 96 cu. μ ; the color index in the "complicated" group, however, averaged 1.11, which is significantly greater than the average of 0.98 in the "uncomplicated" group, and represents definite hyperchromia. In Table 2 we have classified the red cells as simple microcytic, hypochromic microcytic, normocytic, and macrocytic in type. The incidence of macrocytosis in both the "uncomplicated" and "complicated" group was about 50%. When, however, the "complicated" group is divided into those with and without anemia, the incidence of macrocytosis is higher in the anemic group. Further examination of the anemic group reveals that the incidence and the degree of macrocytosis, as well as the degree of hyperchromia, vary directly with the degree of anemia. The incidence of macrocytosis in the "complicated" group without anemia is, however, somewhat lower than in the "uncomplicated" group, apparently due to a higher incidence of simple microcytosis in the former group.

TABLE 2.—INCIDENCE OF THE VARIOUS TYPES OF RED BLOOD CELLS IN 184 ALCOHOL ADDICTS.

Group.	No. of subjects	Hypochromic microcytic.		Simple microcytic.		Normocytic.		Macrocytic.	
		No.	%.	No.	%.	No.	%.	No.	%.
Uncomplicated	25	0	...	2	8.0	11	44.0	12	48.0
Complicated	159	2	1.3	12	7.5	60	37.7	85	53.4
No anemia	62	1	1.6	10	16.1	29	46.7	22	35.4
Anemia	97	1	1.0	2	2.0	31	32.0	63	65.0

TABLE 3.—DATA ON THE "COMPLICATED" GROUP OF ALCOHOL ADDICTS.

Group.	No. of sub-jects.	Anemic, %.	Mean of:		Per cent.			
			Color index.	Size R.B.C.	Hypo-chromic micro-cytic.	Simple micro-cytic.	Normo-cytic.	Macro-cytic.
Polyneuritis	69	52.1	1.15	100.6	...	8.6	40.5	50.7
Stomatitis	48	75.0	1.15	102.1	...	4.1	35.4	60.4
Pellagra	40	65.0	1.11	96.5	2.5	5.0	42.5	50.0
Cirrhosis	30	70.0	1.10	99.0	3.3	16.5	26.4	52.8
Encephalopathy	24	58.3	1.06	102.2	...	8.3	29.1	62.5
Total patients	159	61.0	1.11	101.0	1.3	7.5	37.7	53.4

In Table 3 the "complicated" group is divided into the various listed diseases.* In each disease we have tabulated the frequency of anemia, mean color index, mean size of the erythrocytes, and the incidence of the various types of erythrocytes classified as to size.

* As 85% of the "complicated" group had polyneuritis, we include in the polyneuritic group only subjects having polyneuritis without other stated complications. In the other sub-groups listed in Table 3, subjects are included irrespective of the presence or absence of another listed disease.

The incidence of quantitative anemia in the listed diseases varies from 52.1% in the subjects having only polyneuritis to 75% in the subjects having stomatitis. The average size of the red cells in the whole "complicated" group is slightly greater than normal, corresponding to 96 or 97 cu. μ . This is also true for the various sub-groups except the pellagrins and cirrhotics whose red cells average slightly below the upper limits of normal, corresponding to 92 and 94 cu. μ ., respectively. The averages of the color indices in all five sub-groups show hyperchromia. The incidence of macrocytosis varies from 50% in the pellagrins to 62.5% in the "encephalopaths." The combined incidence of normocytosis and macrocytosis is greater than 90% in all groups except in that having cirrhosis, where this figure totals 79.2%. It is in this cirrhotic group that microcytosis was most frequently present, occurring apparently at the expense of normocytosis; this finding we ascribe to the higher incidence of gastro-intestinal bleeding in this group.

Achlorhydria was found but once in the 25 "uncomplicated" subjects. In the "complicated" group achlorhydria was present in 48.7% of the 119 subjects tested. Joffe and Jolliffe⁶ reported in detail on 105 of these subjects in their study of gastric acidity in alcohol addicts. The additional 14 subjects in no way alter the findings in that study. There is no apparent relationship between achlorhydria and macrocytosis in these "complicated" alcohol addicts, as macrocytosis occurred in 43% of those having achlorhydria and in 52% of those having free acid. There was also no apparent relationship between the degree of anemia and achlorhydria, as those having achlorhydria had an average erythrocyte count of 3,830,000, while those having free acid had an average count of 3,600,000 red cells.

In this study, we have arbitrarily selected the degree of bromsulphalein retention at the end of 30 minutes as an index of liver dysfunction. None of the subjects in the "uncomplicated" group showed a retention of the dye as great as 25%; average 9%. In the "complicated" group 48 of the 99 subjects tested showed a dye retention of 25% or more; average 30%. Macrocytosis occurred in 52% of the group showing a dye retention of 25% or more, as compared with a 58% incidence of macrocytosis in those having a dye retention of less than 25%.

In this study, our criteria for the diagnosis of cirrhosis of the liver require that the ascites cannot be explained on another basis and that visible lateral abdominal veins be present. Our cirrhotic group thus includes only those having liver failure. We have, therefore, considered separately those subjects having and not having an enlarged liver. In the "complicated" group 54% had an enlarged liver, 47.1% of whom had macrocytosis; however, 61% of the "complicated" group whose liver was not enlarged also showed macrocytosis.

In the blood smear examination the outstanding finding was the lack of unusual qualitative changes, except occasionally in subjects having a considerable anemia. The red cells as a rule were of uniform size, and if no quantitative measurements had been done one would not as a rule have called the cells macrocytic. There was a notable lack of anisocytosis, and evidence of regenerative changes was rare. The cells did appear in most instances to be well filled with hemoglobin.

Discussion. It has been shown in this study that anemia is not likely to be found in "uncomplicated" alcohol addicts, but was present in 61% of 159 alcohol addicts having the various named diseases. Macrocytosis of some degree, however, occurred in 48% of the "uncomplicated" group, an incidence only slightly less than the 53% found in the "complicated" group. In two diseases common in alcohol addicts, namely, cirrhosis of the liver and pellagra* (in the alcohol addict), macrocytosis has been frequently reported. In the subjects having liver cirrhosis Wintrobe^{15b} attributed the anemia to the inability of the liver to store the necessary hematopoietic principle. While Wintrobe did not state the incidence of alcoholism in his cirrhotic patients, about 65% of those reported by Rosenberg and Walters¹¹ were known alcohol addicts. That our figures are not peculiar to our laboratory or our group of patients is evident from the fact that in our pellagrins the incidence of anemia and macrocytosis, and the degree of hyperchromia, is practically identical with that reported by Spies and Chinn.¹² The incidence of 53% of macrocytosis in our subjects with liver cirrhosis is lower than that reported by Rosenberg and Walters,¹¹ and higher than the incidence reported by Wintrobe.^{15b} Our figures, therefore, confirm the high incidence of macrocytosis in alcohol addicts having pellagra or liver cirrhosis.

We hesitate, however, to attribute the macrocytosis or macrocytic anemia of our alcohol addicts, either in those having or not having liver cirrhosis, to inability of the liver to store the necessary hematopoietic principle. Our reasons for this belief include the following: 1, Wintrobe's^{15b} observation that mild or moderate cirrhosis is not accompanied by macrocytic anemia. 2, The incidence of macrocytosis is no higher in patients having clinical cirrhosis than in those having the other named diseases, or even very much higher than in alcohol addicts without recognized somatic stigmata of alcoholism. 3, The incidence of macrocytosis is no higher in patients having the greater degree of liver dysfunction than in those having the lesser degree, and is no higher in those having enlarged livers than in those whose livers were not enlarged.

That the hyperchromic macrocytic anemia of alcohol addicts is not due to marked reduction or absence of an intrinsic factor as in

* In endemic Southern pellagra most observers^{5,14} report the anemia, when present, as microcytic.

Addisonian pernicious anemia seems definite. The reasons for this belief include the following: 1, Liver extract or gastric mucosa is not necessary as a rule to produce a remission. In our cases a good diet without liver or kidney, plus vegex,* brewers' yeast* or liver residue lacking the antipernicious anemia factor† in most subjects relieves the anemia within a short time. 2, The anemia is associated, more often than not, with free acid in the gastric contents. 3, Spies and Payne¹³ have reported that the gastric juice of alcohol addicts having pellagra will produce a reticulocyte response in patients in a relapse of pernicious anemia.

We are not prepared to state definitely the cause of the macrocytosis in these subjects, even though alcohol addiction is a factor common to all subjects studied. That it is due to alcohol *per se* seems to us to be untenable in view of the fact that such diseases as pellagra, polyneuritis and cirrhosis of the liver occurring in alcohol addicts are now quite generally believed to be due not to the direct action of alcohol but to associated factors. A history of an irregular or more often of a definitely inadequate diet over varying periods of time was almost a constant finding in our hospitalized subjects. We are therefore inclined to relate the macrocytosis to an extrinsic deficiency of some necessary hematopoietic principle required to maintain normocytosis.

Summary and Conclusions. A quantitative study of the red blood cells in 184 cases of alcohol addiction is reported. Of these subjects, 159 were "complicated" in that they had, in addition to alcohol addiction, one or more of the following diseases: polyneuritis, pellagra, "alcoholic" stomatitis, "alcoholic" encephalopathy, or liver cirrhosis; 25 of these subjects were "uncomplicated" in that they had none of the above listed diseases or other recognized stigmata of chronic alcoholism.

In our subjects, quantitative anemia did not occur in the "uncomplicated" group, but was present in 61% of the "complicated" group. However, macrocytosis was present in about 50% of both groups. Macrocytic anemia in these alcohol addicts was not limited to subjects manifesting pellagra or cirrhosis of the liver, but occurred as well, and in about the same frequency, in subjects having polyneuritis, "alcoholic" stomatitis, and "alcoholic" encephalopathy. There was also no correlation between the frequency of macrocytosis and achlorhydria, severity of liver damage, or the presence of an enlarged liver. In view of these findings we are inclined to regard the macrocytosis of the alcohol addict not as a manifestation of inability on the part of the liver to store a hematopoietic principle but as an extrinsic deficiency of some necessary hematopoietic substance required to maintain normocytosis.

* Courtesy of Vegex, Inc., New York.

† Courtesy of Lederle Laboratories, Inc., New York.

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CONVULSIVE (PENTAMETHYLENETETRAZOL) SHOCK THERAPY IN DEPRESSIVE PSYCHOSES.

PRELIMINARY REPORT OF RESULTS OBTAINED IN TEN CASES.*

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RESULTS obtained by convulsive shock therapy in schizophrenic psychoses have been so impressive that I decided to try a modified treatment upon a case of depressive psychosis. Encouraged by excellent and immediate response, I treated 9 other cases with very favorable results. Since, hitherto, methods of shock therapy successful with schizophrenia have not succeeded with the depressive psychoses, and since almost no similar reports appear in the literature, the 10 cases which are the basis of this preliminary report should be of interest.

Meduna⁵ first used convulsive shock therapy in schizophrenia. Acting upon the observation that convulsive states and the schizophrenic process were apparently biologically incompatible, he perfected a method of inducing convulsions by means of a camphor-like preparation, pentamethylenetetrazol. He has reported results obtained in 74 chronic schizophrenic patients with a disease of 2 to 3 years' duration: 39% were cured; 15% improved; and 46% were unchanged.

Ellery² after a personal visit to Meduna's clinic quotes results in 110 schizophrenic patients: 80% of early cases obtained good remissions, but patients ill longer than 4 years failed to obtain any good results. Friedman⁴ recently quoted Meduna's 110 cases: 96% of cases treated during the first year of the disease were improved

* Presented before Missouri, Kansas Neuropsychiatric Association, Kansas City, Mo., February 15, 1938, and as part of exhibit American Psychiatric Association and American Medical Association, June, 1938.

(this is a 16% increase over Ellery); while less than 8% of cases of 3 or more years' duration showed improvement.

These results are distinctly encouraging and at least equal to the best results reported from insulin shock therapy in early cases. It may be that convulsive shock therapy, because of its simplicity and apparent relative safety, may replace insulin shock therapy. Personally, I still prefer insulin shock therapy in undernourished, acutely excited and paranoid types of schizophrenia; but am using pentamethylenetetrazol for the well nourished, catatonic, hebephrenic and depressed types.

Because of the encouraging results obtained from insulin shock therapy in schizophrenia, attempts were made to relieve depressive psychotic patients, with discouraging results.¹ Furthermore, in all previously tried chemical, endocrine or shock therapy methods such as hematoporphyrin, estrogenic, testicular or pituitary hormones, fever therapy and narcosis, no consistent effect in shortening the course of depressions has been observed.

It was decided to try the effect of pentamethylenetetrazol shock therapy upon a chronic resistant agitated case of depression. The almost immediate, abrupt termination of this very severe depressive psychosis (Case 1) led to further experimentation. The extraordinary improvement in 10 consecutive patients suffering from various types of depressive psychoses was a unique therapeutic experience to me and forms the basis of this preliminary report. The observations to date with the use of convulsive shock therapy in chronic agitated and stuporous types of characteristic depressed affective disorders lead me to believe that we may now have a potent agent for terminating these distressing mental states.

There is practically nothing in the literature so far upon convulsive shock therapy in depressive psychoses. Schächter⁹ noted improvement in 2 cases of hysteria, 4 anxiety states and 3 depressed patients, as well as schizophrenics that he treated with subcutaneous injections of cardiazol (pentamethylenetetrazol). He states that the psychoneurotic patients after use of cardiazol established a better rapport for psychotherapy; he feels that the shock produced a cessation of the anxiety state since his patients were immediately relieved of fear. Schönmehl¹⁰ in using cardiazol as a means of differentiating hysterical convulsions from true epilepsy noted that its use benefited patients suffering from dazed, stuporous or "Dämmerzustand" states.

Montassut and Lemaire⁸ treated depressed states with poly-camphosulphonates in non-shock doses. They found that many depressive symptoms in milder cases disappeared, but the profound depressives were apparently not improved.

The following report is based entirely upon results obtained by pentamethylenetetrazol shock therapy in cases that were all essentially affective depressive psychoses. None of these patients

showed schizophrenic features; 4 were severe involutional melancholic types and the remainder were manic depressive depressed types. Uniformly excellent results have been obtained in all these cases to date. All patients appeared completely relieved of the depressive features of the psychosis within 2 weeks after treatment was begun. No complications from the treatment occurred in any of these patients, yet 3 were past 60 years of age and 1 past 57.

Method. All patients were given exhaustive general physical and laboratory studies, including electrocardiography, prior to shock therapy. Our method of treatment consists of routine alkalization throughout the course to facilitate convulsions. Intravenous injections of pentamethylene-tetrazol, 3 to 12 cc., were given every 2 or 3 days of an average course of 5 convulsive shocks.

Precautions against possible fracture or dislocations are taken by bandaging the head and jaw before treatment and by loosening bed clothing to avoid entanglement of the limbs. Tongue and lips are protected by several cotton dental rolls bound with bandage, inserted between the teeth at the onset of the convulsion. No preliminary explanation of the treatment was given the patients. An attempt was made to reassure the patient and avoid arousal of undue apprehension. The individual intravenous injections were given as quickly as possible. Occasionally, the patient failed to convulse from the initial injection. If this occurred an immediate second dose larger than the first was given. The depressed patient who failed to go into a convulsion was left in an agitated apprehensive state for the remainder of the day or until the next treatment. We considered this an unfavorable reaction.

Immediately following the convulsion and passing of the stupor, patients were urged to enter into ward activities. As a rule the patient appeared less tense, relaxed and was amnesic for events just preceding the treatment. The delirious reaction seen in the schizophrenic patient after convulsive shock therapy was strikingly absent in this series. At times the patient awakened in a jocular euphoric mood or made remarks such as "I've come to life"; "Where am I, things are all changed, more natural"; "I am younger again," and so on. For the remainder of the day patients became more interested and less agitated. Gradually a return to the abnormal, emotional, tense state occurred in about 24 to 36 hours; but after the second, third or fourth injection, the excess anxiety or depression seemed to disappear. Some patients displayed perfectly normal emotivity at the end of treatment; some had residual mild anxiety states and one reacted to a hypomanic excitement for a time.

The psycho-physiologic reactions of such a drastic shock therapy upon the organisms are not as yet in any way understood. The profound circulatory shakeup may be responsible for altering cerebral functioning. On the other hand, the drug may act directly upon the autonomic centers of the brain. The convulsion is probably a symptomatic expression of the profound biochemical cellular metabolic reaction and not necessarily an essential factor in producing the change in the affective tone. Whether organic changes occur

in the brain from its use no one can tell as yet. It appears that we may be inducing physiologically in these cases something equivalent to the more hazardous and radical prefrontal lobotomy of Moniz⁷ and Freeman and Watts.³ Pentamethylenetetrazol action is similar to that of camphor, stimulating vasomotor and respiratory centers. In excessive dosage convulsions are produced resembling picrotoxin poisoning.

Psychologically, the mechanisms of shock therapy offer an interesting possible explanation. In cases of severe depression such as those here described, the patient develops the delusion that he is chiefly responsible for a great many ills and griefs, even for crimes. In all our cases strong self-condemnatory feelings of guilt were present; in several cases, patients accused themselves of murder, loathsome and wicked acts, responsibility for national, social, and family evils. Several expressed the wish to die, one or two had attempted suicide, Case 9 desired to have a prefrontal lobotomy performed, hoping for a fatal outcome. According to Menninger⁶ this conscious wish to die is not entirely genuine, but is a fantasy representing a wish for punishment. The death instinct is never conscious but is manifested indirectly.

This demand of the conscience for punishment was satisfied by the first and subsequent shock treatments. Although the patient received no previous explanation of the shock therapy, he retained unconscious memory of the pain, as shown by requests not to be subjected to later treatments. But having undergone the painful convulsive therapy, he has approached death psychologically, has suffered punishment, has, as it were, proved himself willing to take punishment. His conscience is then freed; and he can allow himself to start life over again free from the compulsive pangs of conscience.

We consider this type of therapy potentially dangerous and not applicable to casual home or general hospital treatment. It should be given only in a well equipped psychiatric department with experienced psychiatric nursing supervision.

The essential facts concerning the patients treated follow:

Case Abstracts. CASE 1. Mrs. J. F., aged 45, had been hospitalized 143 days on account of a severe depressive psychosis. Three members of the immediate family had been psychotic and had become permanent State hospital patients. Prior to present illness the patient had an overactive, elated reaction, following a divorce. "Suddenly I felt a pressure in my chest and became depressed. I knew I'd been cursed." She became very agitated, self-condemnatory and expressed suicidal ideas. After admission, the patient became more agitated and paced the halls: "Call the police, I'm a bad woman. I'm cursed—I have to live in eternal torment. I can never rest. I must give myself up—I'm doomed!" For over 2 months the patient did not talk or respond in any way, became careless of excreta, crawled on the floor and frequently attempted suicide. Commitment papers were arranged for State hospitalization and a grave prognosis given.

At this time convulsive therapy was begun. After the first shock the patient was for a short time responsive and stated: "I feel I am coming to

life." After the second shock: "I want to get up and dress." She also ate in the dining room. After the third and last shock she stated: "I feel so good—I don't know what happened, but isn't it wonderful? I can talk, walk and eat. You have performed a miracle. I don't know how you did it, but I'll never forget it."

The patient merged into a hypomanic state for several weeks, then was dismissed from the hospital and has made a good social adjustment.

CASE 2. Mr. F. S., aged 57, had been hospitalized 527 days, suffering from apparently an intractable type of involutional melancholia. The patient, a bachelor, had an unusually marked mother-fixation. Following a conflict over a possible marriage, anxiety symptoms developed with a minor colon dysfunction. Rapidly a severe hypochondriacal depression developed, requiring special nursing care. The patient refused food, was spoon and tube fed; usually behaved in an infantile manner, was constantly tense, noisy and tearful and at times careless of excreta. Many somatic delusions were present concerning the eyes, bladder, bowels and genitalia. "I'm going blind. I've lost my manhood, my testicles are gone. My bladder is weak. I have to go to the toilet 25 times a night." At times paranoid trends were marked; often profane and vulgar in speech, he required frequent seclusion.

All attempts, even with special nurses, to interest the patient in activities failed, as did psychotherapeutic approach. A variety of treatment procedures were tried: Symptomatic sedation, packs, hydrotherapy, hematorporphyrin injections, insulin shock therapy (27 shocks), fever therapy (9 treatments), testosterone and antuitrin injections, 3 weeks of continuous narcosis and benzedrine sulphate. All were ineffectual in improving the mental state, but a 40-pound weight gain resulted from insulin therapy.

After about 1½ years of such failure, convulsive shock therapy was begun and improvement followed the first convulsion. The patient dressed himself, was less tense and began to take an interest in his personal appearance. In about 36 hours after the first injection, relapse occurred, but within 16 days after the first injection the patient was going outside the hospital unaccompanied. Six shocks were given at 3-day intervals. The patient became entirely coöperative, took an interest in other patients, became friendly with nurses, and gradually gave up his resistant paranoid ideas and somatic complaints. Prior to dismissal, he attended to business affairs and made plans to resume his business. He was dismissed with good insight 22 days after the last shock and has resumed full charge of his business.

CASE 3. Miss R. F., aged 28, following disappointment in a love affair and fear of pregnancy, rapidly developed a depressive psychosis. The patient's sister had had a very similar psychosis requiring about 9 months' psychiatric treatment. The patient was admitted about 1 week after the onset, because of suicidal attempts. An extremely apprehensive, agitated reaction with self-accusatory delusions was present. She believed she was pregnant, had syphilis, and had killed her family. She stated she was responsible for the Sino-Japanese War. Ideas of reference were prominent: that nurses called her a loathsome character, and were spies; that newspapers publicized her record, and so on. Close observation was required because of frequent attempts at self-harm. Much sedative and pack therapy was necessary to control agitation.

Insulin shock therapy with 6 hypoglycemic shocks was given at first, without apparent benefit. Convulsive shock therapy was begun 38 days after her admission. Six reactions at 3-day intervals were given. One good day followed the first reaction. After the third shock the patient began spontaneous occupational activity, wrote letters and coöperated psychotherapeutically. A mood of mild elation followed the sixth treatment. After a period of 2 weeks of psychotherapy, the patient was dismissed with very good insight.

CASE 4.—Miss R. B., aged 37, developed a reactive depressive psychosis apparently precipitated by a disappointment in love. The patient had had a previous depression at 21 years; off work 1 year, she was not hospitalized. The mental status was characterized by marked anxiety; fear of cancer because of weight loss; tearfulness; desire to die; and self-accusatory delusions: "I am unfit to associate with others—the most wicked person on earth—can never get well—I'm going mad. I'm dirty and filthy," and so on. Attempts to ventilate the patient's problem only made self accusations worse.

A course of hematoporphyrin injections made no change in the mental state. Convulsive shock therapy was given. The patient failed to react by convulsions in about half the shocks. After these injections, more apprehension was present. But after 4 good convulsions, all evidence of severe depression disappeared. A mild anxiety state persisted, which was amenable to psychotherapy. The patient was dismissed 3 weeks after shock therapy was begun, in good condition.

CASE 5. Mrs. A. L., aged 60, was admitted in an acutely agitated stuporous state of 2 months' duration. Worry over economic and drouth factors on the farm seemed to start loss of sleep, anorexia and extreme agitation that culminated in an attempt to drown herself in a horse tank. The patient maintained a constant state of tearfulness, usually was mute and required spoon and tube feeding. Extreme self-accusation centered about ideas of an abortion in early life, with notions everything was gone—"family ruined, let me give myself up. I've made all the people sick. I'm so terrible. My son has gone crazy," and so on. At times the patient lay around on the floor and was careless of excreta.

During 2 months' observation, a course of theelin, 10,000 units dosage, and hematoporphyrin had been tried without improvement. The condition appeared to be growing worse. Convulsive shock therapy was begun. Five convulsions were induced at 3-day intervals. After the first convulsion, the patient fed herself for the first time. After the second shock, occupational activities were begun. The patient appeared completely relaxed and wrote letters to the family. From then on she became sociable, pleasant, smiled about everything and attempted to cheer up other patients. Describing her past worries as unimportant, she showed completely normal emotional reactions and was dismissed completely cured, 25 days after shock therapy was begun.

CASE 6. Mr. T. Mc., aged 64, became disinterested in work after financial reversals and an attempt to start business in a new location; he went to live with a son. Paranoid ideas of his son's trying to get rid of him developed. Agitation, insomnia and suicidal threats caused his admission to the psychiatric ward. The mental reactions were characterized by agitation, apprehension, suspicion and refusal to adjust to any activities. He talked about an unhappy home life, past reversals and fears he would be poisoned or sent to the State hospital, since no one was interested in helping him. Numerous somatic delusions were present. He thought everyone about him had syphilis.

After 12 days of symptomatic treatment no evidence of improvement was noted and convulsive shock treatment was begun. The patient was extremely apprehensive over the treatment. Four convulsive shocks were given at 3-day intervals. After the first shock the patient joked and became less tense. He continued fearful of each injection but entered into ward activities, became jocular and no longer delusional. Because of angina-like symptoms following the fourth injection, no more shocks were given. Electrocardiogram tracings were normal. The mental reactions continued normal and the patient was dismissed apparently well, 2 weeks after shock therapy was begun.

CASE 7. Mrs. E. F. C., aged 49, after a series of emotional shocks and a guilt conflict over a prolonged sexual problem, became depressed. Ideas of reference—self accusations and a progressive paranoid trend—had been present for over a year. Because of loss of interest, brooding, withdrawal from active contacts and suicidal threats the patient was brought to the hospital.

Under observation for 30 days, during which time active estrogenic therapy was carried on, the patient continued to react with almost constant anxious and depressed attitudes. A strong religious drive with ideas of having committed the unpardonable sin, self-accusation over her recent marriage, with delusions of persecution referred to the husband's relatives, characterized the mental content. Somatic delusions related to syphilis and the pelvic organs were also present.

Convulsive shock therapy was advised; the patient reacted to convulsions with each injection. After the third injection, the patient began active occupational interests, laughed at jokes, and stated her past ideas were like a dream. Normal letter writing was begun; the patient accepted the treatment as beneficial and lost all evidence of former despondency. After the sixth injection the patient appeared entirely well. Two more weeks, hospital observation for reeducative psychotherapy was carried out and the patient dismissed.

CASE 8. Mrs. L., aged 35, had had a depressive breakdown at 21 years of age; gave up teaching for 9 months, and recovered. The present attack, of 4 months' duration, had begun after the death of her father. Psychogenic conflicts over a childless marriage, incomplete sexual adjustment and fear of pregnancy were also present. Progressive loss of interest, agitation, insomnia and self condemnatory ideas with suicidal threats caused hospitalization. The mental status was characterized by extreme agitation, and apprehension with panics that required sedative pack therapy and seclusion: "I can't stay here—no one can help me—I'm losing my mind—I'm responsible for my father's death," and so on. Two weeks' symptomatic sedative therapy, hydrotherapy and all attempts to establish a rapport or to interest the patient were unavailing. Exceedingly close observation was necessary on account of suicidal threats.

Convulsive shock therapy was begun. After the first convulsive seizure the patient dressed spontaneously, appeared relaxed and was cheerful in the afternoon. She stated that she "felt good." Slight relapses to the previously tense and agitated states occurred. After the second seizure, the tenseness and agitation again disappeared. The patient gradually became more and more coöperative in occupational and recreational therapy. The self-accusatory ideas disappeared and a constructive future program was planned. The patient was dismissed entirely well 48 days after shock therapy was begun.

CASE 9. Mr. W. S., aged 30, had a bad family history of depressive states. The patient had had two previous depressive attacks lasting 8 months to 1 year and in the last one had attempted suicide by gas poisoning. Following this, the patient had adjusted fairly well but had never recovered. One month prior to hospitalization he became acutely depressed and again attempted suicide. He also attempted to persuade a neurosurgeon to perform a prefrontal lobotomy, hoping for a fatal outcome. Under observation the patient was extremely restless, constantly complaining, appealing for help and threatening suicide. In panic states—"I can't stand it, give me a shot, knock me out, I'm losing my mind"—sedative packs were necessary.

Convulsive shock therapy was started and 7 injections given. The patient became relaxed and, after the second injection, coöperated well with occupation. Gradual improvement followed each injection. Financial strin-

gency and an unstable wife along with the patient's insistence that he was able to return to work led to his dismissal against advice. Following dismissal the patient found he had lost his position and when last seen was reacting at the level of an anxiety neurosis. The intense depressive features, however, seemed entirely gone. This was an incomplete recovery and the poorest result obtained of the entire group; yet, a very definite and marked improvement, to a point that psychiatric hospitalization was no longer necessary, followed the convulsive therapy.

CASE 10. Mrs. B. E. H., aged 65, had been under treatment for 4 months in a psychiatric hospital in 1935 and 1936 on account of an agitated depression. This was characterized by ideas of self unworthiness, "lost soul," unpardonable sin and suicidal desire. Removal of focal infection, hematoporphyrin injections and estrogenic therapy along with symptomatic sedation resulted in an apparent improvement sufficient to permit the patient to adjust outside an institution, but complete recovery did not occur. The patient's daughter gave up school teaching to care for her. Frequent long trips were taken, but the patient never resumed social activities or charge of her household responsibilities. After 2 years there was no evidence that the depression would disappear.

The patient was returned for pentamethylenetetrazol shock therapy. Improvement followed each convulsive seizure and a mild hypomanic reaction occurred after the first three shocks. She developed active interest in the ward activities, and is still under hospital observation but the improvement seems to be following as noted in the other patients.

Comment on All Cases. The consistent change in the affects in all 10 of these severely depressed patients following convulsive shock leaves but little doubt that the treatment was responsible for the change.

A number of recommended therapies for depressive states (including insulin shock therapy) had been tried in the majority of these cases without influencing the course of the depression in any case before convulsive shock therapy was instituted.

The regularity of improvement within 2 weeks after pentamethylenetetrazol treatment was begun, even in severe types in the presenile period (Cases 2, 5, 6 and 10), speaks for the specificity of the method.

While we regard the method as potentially dangerous, particularly in the aged cases, no complications have resulted. We believe this treatment should be administered only under efficient psychiatric hospitalization and nursing protection. In older patients, careful investigation of cardiovascular function should precede therapy, which should not be instituted in cases showing myocardial or vascular disease.

We cannot explain the mechanism of recovery in these cases, but it is undoubtedly physiologic in nature and not psychologic. The circulatory change in the cerebrum resulting from the convulsions seemed to have some direct effect upon the emotional centers of the brain, alleviating anxiety and depression. The effect seemed strikingly similar to that described by the authors recommending prefrontal lobotomy.

Sufficient time has not elapsed to determine delayed after-effects of the treatment or incidence of relapses. As far as could be determined, the recovered patients continue to be stable and normal.

Conclusions. Ten consecutive severe depressive psychotic patients have all been relieved by pentamethylenetetrazol shock therapy.

This method has more consistently shortened the depressive psychosis than any method heretofore described.

It is probable that the profound temporary change in cerebral circulation from induced convulsions alters physiologically the pathologic anxiety and depressive affective reactions. The result obtained is not entirely psychologic.

This method should be given further experimentation. It appears to be reasonably safe, even in older patients, but careful cardiovascular examination should precede its use. Its potential danger precludes its use for the present in general practice. It should be given only in well equipped psychiatric departments under skilled medical and psychiatric nursing supervision.

This treatment offers considerable hope of rapidly relieving the legions of suffering melancholiacs. There is also reason to believe the method may likewise become useful in severe anxiety psychoneuroses.

Eleven more patients, a total of 21 seriously depressed, have undergone convulsive shock therapy up to June 1, 1938. All of these showed marked improvement within 2 weeks after convulsive shock treatment began. Eight patients were past 55 years. No treatment complications were observed. One of involutional type had been a State hospital patient for over 2 years. All made social or complete recoveries. One relapsed in an acute manic excitement and was committed to a State hospital.

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BOOK REVIEWS AND NOTICES.

PAVLOV AND HIS SCHOOL. The Theory of Conditioned Reflexes. By PROFESSOR Y. P. FROLOV, M.D., Member of the All Union Institute of Experimental Medicine, Moscow. Pp. 291; 27 illustrations. New York: Oxford University Press, 1937. Price, \$4.00.

PAVLOV'S "Lectures on Conditioned Reflexes" has been so widely read even by those outside the scientific field and it covers the subject so clearly and adequately, that the indication for this early review of the material may well be questioned. The bulk of Dr. Frolov's book constitutes such a review and offers at least a partial answer to the query. In the new light which the later work of Pavlov and his school has thrown upon the interpretation of their older results such a reappraisal finds its best excuse. For most readers, however, the last chapter, an admirable essay in biography, is the part of the book that will be reread, for the sake of which they will not grudge it shelf room beside the work of the master who inspired it.

G. McC.

THE ANEMIAS. With Special Reference to Pernicious Anemia and the Use of Liver Extracts and Supplementary Factors in the Treatment of Anemias. Supplement. Blood Morphology in Diagnosis. A Series of Six Articles Reprinted from The Physician's Bulletin. Pp. 98; 7 colored plates. Indianapolis: Eli Lilly and Company, 1938.

THIS anonymous booklet has obviously been prepared by or with the help of a trained hematologist. It presents much useful and apparently accurate information, several good colored plates of characteristic blood smears, a section on diet in the anemias, and tables of standards and differential diagnoses. The advertising in the text, apparently essential to a "house publication," is limited to a comparatively few pages.

E. K.

PEDIATRIC SURGERY. By EDWARD C. BRENNER, A.B., M.D., F.A.C.S., Director of Surgery, Riker's Island and Detention Hospitals; Attending Surgeon, Midtown Hospital, etc. Pp. 843; 293 illustrations. Philadelphia: Lea & Febiger, 1938. Price, \$10.00.

THIS volume, in which the author was assisted by well known workers in special fields, emphasizes the surgical lesions of pediatric practice. Special attention is given to diagnosis, indications for operations and end-results. In numerous instances operative procedures are discussed in detail and the important facts in regard to preoperative and postoperative treatment are thoroughly reviewed. The volume omits orthopedic conditions and operations for "these are well considered in many textbooks." The work is essentially in amplification of the author's lectures at the New York Post-Graduate Medical School of Columbia University.

There are 9 parts and 51 chapters covering nearly the entire field of general surgery. It may well be wondered at first, when so much of the diagnostic and therapeutic portion of the volume is a reiteration of material found in standard textbooks of surgery, why it should all have been included in this volume? However, the subject matter in this form of presentation reads so well that the Reviewer feels justified on the whole in commending

the method of presentation. Here and there in the text statements are made which are not in agreement with the Reviewer's surgical opinions. An instance of this is in the discussion of the "Choice of Incision" for acute appendicitis. There are many surgeons who prefer the pararectus incision for chronic appendicitis, but prefer the McBurney incision for acute appendicitis.

The work is voluminously illustrated with good clear illustrations. Occasionally an illustration appears to have been made from some one past the pediatric age, as in Figure 130.

Although the work is in reality a textbook of surgery it includes so much that it is of practical value in the treatment of surgical diseases of children that it should prove a valuable addition to surgical practitioners.

I. R.

DIE STÖRUNGEN DER SEXUALFUNKTION BEI MANN UND WEIB. VON DR. LUDWIG CHIAVACCI, Wien, Mit einem Geleitwort von PROF. DR. OTTO PÖTZL. Pp. 146. Wien: Franz Deuticke, 1938. Price, Paper, M. 4.60; Bound, M. 5.40.

THIS monograph should prove to be indispensable to those physicians who are called upon to deal with functional sexual difficulties, as diagnosis and therapy rest on the firm basis of physiology and pathology. The author purposely avoids the psychoanalytic pitfalls of psycho-sexual disturbances and very wisely states that the organic-physiologic basis of these disturbances must first be recognized and evaluated before the problem is approached from the psycho-therapeutic viewpoint.

B. H.

A TEXT-BOOK OF PATHOLOGY. Edited by E. T. BELL, M.D., Professor of Pathology in the University of Minnesota, Minneapolis, Minn. Pp. 894; 412 illustrations and 2 colored plates. Third Edition, enlarged and thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, \$9.50.

IN this third edition there are 127 more pages, more references have been added, and there are 62 excellent new illustrations. The general plan of the previous editions has been retained, but revisions in the text have been made throughout. The presentation is systematic and clear, heavy print attracts the eye to the important headings, and illustrations derived from the practice of pathology are very convincing. These modifications should greatly increase the usefulness of this textbook in fulfilling the aims of its author to furnish students of pathology with a sound basis for clinical medicine.

I. Z.

THE TRUTH ABOUT CHILDBIRTH. Lay Light on Maternal Morbidity and Mortality. By ANTHONY M. LUDOVICI. Pp. 294. New York: E. P. Dutton & Co., Inc., 1938. Price, \$2.50.

THE author, a well known sociologist of England, advances in this book the theory that childbirth should not be regarded in other than the light of a consciously pleasant experience. In developing the thesis he discusses the factors which have influenced a state of mind among women and physicians that pregnancy is a disease of 9 months, with delivery as the catastrophic climax to the disease. Simultaneously he brings out support to favor directly his contention that the frequent abnormalities of pregnancy and delivery are not essential and can be removed.

The first part of the book discusses the influence of increasing intelligence,

the feministic trend of thought and the economic conditions of the world today on reproduction, and describes the physiology of normal childbirth.

The second part discusses those conditions which conflict with painless and pleasurable birth. These include the factor of age at the time of delivery of the first child, the effect of late marriages, athleticism, miscegenation, the mixture of types and statures and nutritional deficiencies of the present day diet.

Further the author describes the primitive postures in childbirth, the relationship of modern habits of life on delivery and the demand for and effect of analgesics and anesthetics in labor. The book is profusely documented in a remarkable review of the literature dealing with the sociologic aspects of reproduction.

There are many intriguing statements and deductions brought out with which all obstetricians probably will not agree; but it may certainly be admitted that the text is extremely interesting in the discussion of many problems faced in present day obstetrics. P. W.

HEMORRHOIDS. By MARION C. PRUITT, M.D., L.R.C.P., S. (Ed.), F.R.C.S. (Ed.), F.A.C.S., Atlanta, Georgia, Associate in Surgery, Emory University School of Medicine; Proctologist, Grady, Crawford W. Long Memorial, and Georgia Baptist Hospitals, etc. Pp. 170; 73 illustrations. St. Louis: The C. V. Mosby Co., 1938. Price, \$4.00.

THE author, regarding the treatment of hemorrhoids as still a live subject, attempts here to describe and evaluate the various methods of treatment. The first part of the book discusses the embryology, surgical anatomy and physiology of the lower rectum and anal canal. Then follows a section on examination of the patient and the instruments used. In speaking of anesthesia, the author recommends a general anesthetic or a local infiltration anesthesia with nupercain 1 to 1000 solution. He believes that spinal anesthesia is indicated in only certain selected cases, and caudal or transsacral block is a tedious and time-consuming method. He briefly discusses the pathology of hemorrhoids and classifies them in what appears to the Reviewer to be an unnecessarily complicated manner. Considering treatment, he recommends immediate operation for thrombosed external hemorrhoids, but is in favor of conservative therapy for inflamed or strangulated internal hemorrhoids. He reviews the history of injection treatment and describes his own technique. He uses 5 to 12% solution of carbolic acid in a vehicle of equal parts glycerin and water and injects 3 to 10 drops into the center of each hemorrhoidal mass. If the injections are submucous he uses 1 to 6 cc. of 5 to 10% solution of phenol in vegetable oil. He recommends that all the internal hemorrhoids be injected at each treatment through a short tubular speculum. When injecting into the center of the mass, the needle is allowed to remain in place for about a minute after injection. The author believes that edema "occludes the needle puncture in most cases immediately following the withdrawal of the needle and tends to prevent backflow of the solution." Injections are given 5 to 10 days apart and an average of 4 to 5 treatments are given. Pruitt places recurrences following injection at from 15 to 20% as compared with 5 to 8% recurrence following operation. In his chapter on operative treatment of internal hemorrhoids he describes his own technique as well as the well-known operations of Buie, Lockhart-Mummery, Tuttle and Whitehead. He mentions the use of galvanism and of high-frequency currents in the treatment of hemorrhoids only to condemn them. The book contains many original illustrations, some in color. It will probably be useful to those who are interested in proctology. L. F.

CHRISTIANITY AND SEX. By RICHARD C. CABOT, M.D. Pp. 78. New York: The Macmillan Company, 1938. Price, \$1.00.

CONTINUING a long and distinguished career in scientific medicine, the author has in recent years also contributed notably toward illuminating the borderline between the physician and his patient. "Honesty," "The Layman's Handbook of Medicine," "What Men Live By," "The Meaning of Right and Wrong," and "The Art of Ministering to the Sick," are not only much needed expositions of an experienced and intelligent, 20th century Puritan's principles of morals but also valuable interpretations of medical advances in terms understandable by the laity. This, his latest work, frankly and firmly emphasizes that the Christian spirit must be the guide to the solution of the problem of sex. Knowledge of sex hygiene is of little help; medical men and nurses are no more or no less chaste than others of similar intelligence. Throughout the 4 chapters he emphasizes that a Christian attitude is of more importance in sex matters than set rules of conduct, that sex relationships have as important spiritual as physical sides, that life, "the greatest word in the Christian vocabulary," may be had more abundantly by the fullest union of body and spirit. Available reinforcements of "the consecrated affections" are suggested; but attempts to deal with the "original sin" of desire are, perhaps necessarily, incomplete. If the average person could attain the intense religious spirit of the writer, not only would sex cease to trouble but the world would be a very different and better place to live in.

E. K.

A TEXTBOOK OF CLINICAL PATHOLOGY. Edited by ROY R. KRACKE, B.S., M.D., Professor of Pathology, Bacteriology and Laboratory Diagnosis; Chairman of the Department, Emory University; Pathologist to the University Hospital. With the assistance of 11 Additional Contributors. Pp. 567; 205 illustrations and 31 plates (19 in color). Baltimore: William Wood & Co., 1938. Price, \$6.00.

THIS is an excellent, practical, comprehensive, up-to-date textbook of clinical laboratory diagnosis, by an all-Southern group of teachers representing the Universities of Georgia, Tennessee, Texas, Alabama, Louisville and Arkansas, Emory, Vanderbilt and Tulane Universities, and The Medical College of the State of South Carolina. The Reviewer, trying hard to find something to criticize, suggests that the Dare hemoglobinometer is given a less critical rating than it deserves (p. 117), the figures illustrating the blood picture of pernicious anemia "in remission" (p. 198) should be omitted, raised to normal or labelled "Blood Picture in Unsatisfactory Remission or Partial Relapse" and the figures (pp. 199 and 200) illustrating "Blood Picture under Liver Therapy" should be entitled "Blood Picture at End of First Week of Liver Therapy." The chapters are well correlated and documented. The index, figures and plates are good. The book is highly recommended for students, interns, laboratory technicians and practising physicians.

T. F.-H., JR.

BILE. ITS TOXICITY AND RELATION TO DISEASE. By O. H. HORRALL, M.D., PH.D., F.A.C.S., Department of Physiology, The University of Chicago. With a Foreword by A. J. CARLSON, M.D., University of Chicago. Pp. 434. Chicago: The University of Chicago Press, 1938. Price, \$4.00.

THIS monograph, the second on the bile to be published in this country during the year, aims to summarize and analyze the physiologic and toxic actions of bile as revealed by past observations and experiments. The author states that "no critical summary of our modern knowledge of the

composition of bile and its relation to disease is available." Surely Ivy's excellent critical summary of the subject in *Physiological Reviews* must have been overlooked.

There are 27 chapters, a bibliography and an index. An attempt is made to cover every aspect of the subject from the "History of Bile" to the "Therapeutic Effects of Bile Acids." The volume reviews a great mass of experimental and clinical observations. As an encyclopedia of the literature on the subject of the bile, it will prove useful to workers in the field; but to those whose knowledge of the subject does not permit them to pass judgment on reviews of material, the volume may prove to be misleading. This is especially true of chapters such as the one on "Origin of the Bile" where many conflicting observations are reported and only rarely does the author state his opinion, based upon his work on the bile and his judgment as an investigator.

The bibliography consists of 2177 references, and, therefore, is the largest available. The work will prove very valuable to anyone interested in the many problems of the bile for to them it will be a *vade mecum* of the literature on the subject.

I. R.

NEW BOOKS.

The British Encyclopedia of Medical Practice. Including Medicine, Surgery, Obstetrics, Gynæcology, and Other Special Subjects. Vol. 7. *Hyperchlorhydria to Leucorrhœa and Other Non-hæmorrhagic Vaginal Discharges.* Under the General Editorship of SIR HUMPHRY ROLLESTON, Bt.G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge, etc. With the assistance in a consultative capacity of F. R. FRASER, M.D., F.R.C.P., G. GREY TURNER, D.Ch., M.S., F.R.C.S., JAMES YOUNG, D.S.O., M.D., F.R.C.S. Ed., F.C.O.G., SIR LEONARD ROGERS, K.C.S.I., M.D., LL.D., F.R.C.P., F.R.C.S., F.R.S., and F. M. R. WALSHE, O.B.E., M.D., D.Sc., F.R.C.P. Pp. 759; 171 illustrations. London: Butterworth & Co., 1938. Price, \$12.00.

Among the more important articles in this volume are those on Impetigo (22 pages), Influenza (18 pages), Intelligence Tests (12 pages), Joint Diseases (43 pages), Kala Azar (36 pages), Surgical Diseases of the Kidney (34 pages), Labor (178 pages), Larynx Diseases (29 pages).

Injection Treatment of Varicose Veins and Hemorrhoids. By H. P. MCPHEETERS, M.D., F.A.C.S., formerly Director of the Varicose Vein and Ulcer Clinic, Minneapolis General Hospital; Attending Physician, New Asbury, Fairview and Northwestern Hospitals, Minneapolis, and JAMES KERR ANDERSON, M.D., F.A.C.S., Instructor in Surgery, University of Minnesota School of Medicine; Fellow, American Proctologic Society, etc. Pp. 315; 82 illustrations. Philadelphia: F. A. Davis Company, 1938. Price, \$4.50.

The Doctrine of Signatures. A Defence of Theory in Medicine. By SCOTT BUCHANAN. Pp. 201. New York: Harcourt, Brace & Co., 1938. Price, \$2.75.

Polski Przegląd Radiologiczny, Tom. XII, Nr. 3/4. Edited by DR. W. ZAWADOWSKI, Warsaw. Pp. 693; many illustrations. Warsaw: Nakl. Polskiego Lekarskiego Tow. Radio. I. Fizjoterap., 1937.

Salaries in Medical Social Work in 1937. By RALPH G. HURLIN, Director, Department of Statistics, Russell Sage Foundation. Pp. 34. New York: Russell Sage Foundation, 1938. Price, 20c.

The Fight for Life. By PAUL DEKRUIF. Pp. 342. New York: Harcourt, Brace & Co., 1938. Price, \$3.00.

- Lehrbuch der Pharmakologie, Toxikologie und Arzneiverordnung.* Unter Mitarbeit von Prof. Dr. med. et rer. nat. HEDWIG LANGECKER, Dr. med. FRANZ HENDRYCH, Dr. med. et rer. nat. et mag. pharm. KARL KLIMESCH und Dr. rer. nat. et Dipl. Ing. HANS WEDEN. By DR. MED. EMIL STARKENSTEIN, o. ö. Prof. der Pharmakologie und Pharmakognosie an der deutschen Universität in Prag. Pp. 758; 40 illustrations. Wien; Franz Deuticke, 1938. Price, Paper, M. 20; Bound, M. 23.
- Zum Krebsproblem und Verewandten Gebieten.* Infektion, Regeneration, Zellmutation, Befruchtung. Von DR. FRITZ NIEDERMAYER, Chefarzt und Leiter der chirurgischen Abteilung des Krankenhauses Passau. Pp. 166. Wien: Franz Deuticke, 1938. Price, Paper, M. 5; Bound, M. 7.
- Vitamin B₁ (Thiamin) and Its Use in Medicine.* By ROBERT R. WILLIAMS, Sc.D., of the Bell Telephone Laboratories, New York City, and TOM D. SPIES, M.D., Associate Professor of Medicine, University of Cincinnati. Pp. 411. New York: The Macmillan Company, 1938. Price, \$5.00.
- Sulfanilamide Therapy of Bacterial Infections.* With Special Reference to Diseases Caused by Hemolytic Streptococci, Pneumococci, Meningococci and Gonococci. By RALPH R. MELLON, M.D., DR. P.H., D.Sc. (Hon.), Director, Institute of Pathology, The Western Pennsylvania Hospital, Pittsburgh; PAUL GROSS, M.D., Pathologist to the Institute; and FRANK B. COOPER, Research Chemist to the Institute. Pp. 398; 16 illustrations. Springfield, Ill.: Charles C Thomas, 1938. Price, \$4.00.
- The Construction of Vulecanite Applicators for Applying Radium to Lesions of the Buccal Cavity, Lips, Orbit and Antrum.* By DESMOND GREER WALKER, M.A., M. DENT. SC., M.B., B.Ch., Assistant Dental Surgeon to the Royal Dental Hospital; Dental Registrar at the Middlesex Hospital, etc. Foreword by W. WARWICK JAMES, O.B.E., F.R.C.S., L.D.S. Pp. 61; 2 illustrations and 22 plates. London: John Murray for the Middlesex Hospital Press, 1938. Price, 5/-.
- A Bibliography of The Works of Ambroise Pare: Premier Chirurgien & Conseiller du Roy.* By JANET DOE, Assistant Librarian of the New York Academy of Medicine. Pp. 265; 30 illustrations. Chicago: The University of Chicago Press, 1937. Price, \$5.00.
- Clinical Roentgenology of the Digestive Tract.* By MAURICE FELDMAN, M.D., Assistant Professor of Gastroenterology, University of Maryland; Associate Roentgenologist, Sinai Hospital; Assistant in Gastroenterology, Mercy Hospital, Baltimore. Pp. 1014; 358 illustrations. Baltimore: William Wood & Co., 1938. Price, \$10.00.
- The Harvey Lectures, Series XXXIII.* Delivered under the Auspices of the Harvey Society of New York, 1937-1938. Under the Patronage of the New York Academy of Medicine. By Drs. SELIG HECHT, EINAR LUNDESGAARD, CECIL K. DRINKER, JOHN P. PETERS, PHILIP BARD, WENDELL M. STANLEY, F. C. KOCH, HARRY GOLDBLATT. Pp. 275; 60 illustrations. Baltimore: The Williams & Wilkins Company, 1938. Price, \$4.00.
- Clinics on Secondary Gastro-intestinal Disorders; Reciprocal Relationship.* By JULIUS FRIEDENWALD, M.D., Professor Emeritus of Gastroenterology, THEODORE H. MORRISON, M.D., Clinical Professor of Gastroenterology, and SAMUEL MORRISON, M.D., Assistant Professor of Gastroenterology, University of Maryland, School of Medicine. Pp. 251. Baltimore: William Wood & Company, 1938. Price, \$3.00.
- Memorandum Book of a Tenth Century Oculist* for the Use of Modern Ophthalmologists. A Translation of the Tadhkirat of Ali ibn Isa of Baghdad (cir. 940-1010 A.D.), the most complete, practical and original of all the early textbooks on the Eye and Its Diseases. The First Edition in English, by Casey A. Wood. Pp. 260; 21 illustrations. Chicago: Northwestern University, 1936. Price, \$8.00.

NEW EDITIONS.

Diseases of Women. By Ten Teachers, Under the Direction of CLIFFORD WHITE, M.D., B.S. (LOND.), F.R.C.P. (LOND.), F.R.C.S. (ENG.), F.C.O.G. Edited by SIR COMYNS BERKELEY, CLIFFORD WHITE and FRANK COOK. Pp. 492; 159 illustrations and 7 colored plates. Sixth edition. Baltimore: William Wood & Co., 1938. Price, \$6.00.

Clinical Atlas of Blood Diseases. By A. PINEY, M.D., M.R.C.P., Consulting Physician, International Clinic, Tunbridge Wells; Assistant Physician, St. Mary's Hospital for Women and Children, etc.; and STANLEY WARD, M.D., M.R.C.P., Physician, The Royal Cancer Hospital, London, and Princess Beatrice Hospital. Pp. 127; 42 plates (38 in color). Fourth edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1938. Price, \$4.50.

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PROGRESS OF MEDICAL SCIENCE

PATHOLOGY AND BACTERIOLOGY.

UNDER THE CHARGE OF

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PRIMARY CARCINOMA OF THE LUNG.

DURING the past few decades, clinicians, pathologists and medical statisticians have all been focusing their attention on carcinoma of the lung as a condition deserving of intensive investigation. The results of this scrutiny are to be found in the mass of literature which has been accumulating at an ever-increasing rate, and which has been responsible for a marked change in attitude toward this peculiarly interesting condition. Though all phases of the question have been extensively studied since the recording of Morgagni's case⁶⁴ in 1761 and Bayle's "phthisie cancéreuse"⁷ in 1810, it may still be difficult for the casual reader to obtain a clear picture of the subject as a whole, being faced on the one hand by detailed compilations of data and on the other by brief case reports, or writings dealing with a limited or narrow phase of the problem. Textbooks are likewise of little help, particularly those of a clinical nature which tend to dismiss the matter with extreme brevity, merely emphasizing the rarity of the disease and the difficulties associated with the diagnosis. But it must be borne in mind that in reviewing briefly a subject such as bronchial cancer, little can be done other than to trace the evolution and moulding of opinions regarding the condition. This is in sharp contrast with the field of experimental medicine where controlled observations point to incontestable conclusions. No attempt has been made in the present paper to review the whole literature of carcinoma of the lung. References will be made only to those publications which would appear to be the most authoritative and which most clearly demonstrate the trend of modern thought.

Incidence. Carcinoma of the lung can no longer be considered a rare condition as was frequently stated, even as late as 1922.⁶ The

present incidence of the disease has attained a high position among all neoplasms. Barron⁶ found carcinoma of the lungs and bronchi ranked sixth among all malignancies, while Rosahn⁷² placed it fifth. Rosedale and McKay⁷³ found carcinoma of the lung the third-commonest cancer encountered in a series of 466 cases of malignancy of all types. Brines and Kenning¹² placed the lung second to stomach as a seat of primary malignant neoplasms in their necropsy material and fifth in their surgical specimens. Simpson⁸² found pulmonary cancer constituted 3.7% of his autopsies, while other figures vary from about 1 to 4% of all postmortems.^{9a,b} From the observations made in the Department of Pathology at the University of Toronto over a 10-year period ending in 1936, the lungs and bronchi proved the third-commonest site for malignant epithelial tumors as seen at autopsy, being preceded only by the large bowel (including the rectum) and the stomach. Indeed, 1.17% of all autopsies were cases of bronchial cancer, which in turn constituted 17% of all cases of carcinoma. Though it is difficult to determine the actual present-day incidence of the disease, it must be considered comparatively common, while pulmonary tumors of other than a carcinomatous nature are now looked upon as being relatively rare.²¹

Nearly all are agreed that the condition is encountered with greatly increased frequency, and this has raised the controversial question of whether the increase is actual or apparent. In a survey of much of the European literature on the subject, Bonser^{9b} found a reported increase in the condition in 32 instances, a slight increase in 5 and no increase in only 8. Wahl,⁹³ from 1895 to 1927, found an increase in the incidence of cancer of the lung from 0.44 to 1.69% of all autopsies; Duguid,¹⁹ from 1885 to 1926, observed an increase from 0.24 to 2.57%; Kikuth,⁴⁷ from 1889 to 1923, showed an increase from 0.02 to 0.86% and Barron,⁶ from 1889 to 1921, an increase from 0 to 0.9% and so on. The increased frequency with which the disease is recognized is further emphasized when one considers that Adler,¹ in 1912, was able to collect but 374 authenticated cases, whereas a complete present-day summation would number thousands with some reports, including a hundred or more from a single source.

A few investigators believe that no increase has occurred in the incidence of carcinoma of the lung. Thus, Bonser^{9a,b} was unable to demonstrate any change in the incidence of the condition in relation to total autopsies, total cancers, or hospital admissions at the Leeds Infirmary. Though this worker did observe that the highest incidence occurred during the 5-year period ending in 1932, this was only slightly in excess of the incidence for the 5 years from 1908 to 1912. Similarly, Passey and Holmes,⁶⁸ in a carefully controlled analysis of the available statistics from some of the teaching hospitals of Great Britain, found no increase in the incidence of carcinoma of the lung in 8 instances and a variable increase in 8 others. These writers considered that the increased incidence found in these latter was the result of special circumstances and did not indicate a real change. The statistics from several of these hospitals, from which it was deduced that no increase had occurred, had previously been reported in a different form¹⁹ and had been considered indicative of an actual increase.

Despite such reports as the foregoing, the great majority of authors

are agreed that the condition is now seen more commonly than formerly. Most of them, however, consider the increase purely apparent and offer a variety of reasons in explanation of this. Important among these are the increased span of human life, and increased interest in the condition stimulated by both improved diagnostic equipment and the hope of carrying out successful intrathoracic surgical procedures.^{4,14,21} Other important factors are fashion in diagnosis⁴⁶ and the changed attitude of the pathologist who now recognizes to be actually primary carcinomata pulmonary lesions formerly considered metastatic, sarcomatous or inflammatory.⁵

It is obvious that increase in longevity, by allowing more people to reach the cancer age, should be accompanied by an increase in cancer in general. That this might be considerable can be appreciated when it is realized, as has been pointed out by Fried,^{29c} that the average span of life from the time of Tut-Anhk-Amen to the discovery of America was only 18 years, at the time of the French Revolution (1789-1799) 33 years, and at the time of the Civil War (1861-1865) still only 45 years.³³ At present the average length of life is in the neighborhood of 58 years. Corresponding with this increase in longevity, an apparent increase in the incidence of cancer in general has occurred, as pointed out by Wells,⁹⁵ who indeed considers that a "high crude cancer death rate is evidence of a good state of public health." Wells further states that cancer has probably increased only to the extent that people are kept from dying of other conditions. Despite the fact that graphs can be prepared to show a parallellism between the increased life span, increase in cancer in general and increase in cancer of the lung in particular (as has been well done by Hrubby and Sweany⁴¹) many observers have found that the increase in lung cancer has far outstripped the increase in all others,^{72,94b} and this precludes an explanation of the increase of cancer of the lung on the basis of increased expectancy of life alone.

There can be no doubt that clinical interest has been stimulated by the development of Roentgen ray, bronchoscopic and biopsy techniques, and by the more consistent recognition of bronchial carcinomata by the pathologist at autopsy. The effects of this interest, however, on autopsy statistics must be indirect and possibly slight, depending upon increased zeal in obtaining autopsy permission, and also, the keeping of patients with such lesions in hospital up to the time of death at the expense of many of the less interesting and better understood cases.⁸²

Although Simpson⁸² doubted that any improvement in clinical diagnosis had occurred, and indeed found the greatest clinical error in the year 1924, the vast majority of investigators have noticed a great change. Bonser^{9a} noted an increase in the frequency with which the clinical diagnosis was made from 0.127 to 0.253 % of all hospital admissions over a period of 41 years, while the incidence at autopsy remained constant. Weller,^{94c} in 1913, found a correct diagnosis had been made in 11 % of his cases; none of those reported by Scott and Forman,⁷⁸ in 1916, were recognized clinically; but Brines and Kenning,¹² in 1937, found a correct diagnosis had been made in 73 % of their series. One reason for this improvement in diagnostic skill is the many additional aids available to internists.¹⁶ Actually the value of the Roentgen ray, with or without the use of iodized oil, is questioned by some,⁵⁵ and

Fishberg^{26b} considers a careful history and physical examination of much greater importance, particularly in the recognition of early cases. Histologic studies on sputum and pleural fluids are occasionally of assistance, but are of more use in ruling out tuberculosis and other infections.^{94b} Such examinations may also prove misleading, as is clearly shown in the case reported by Mills and Mumey⁶² which was originally mistaken for a case of *Entamoeba histolytica* infestation. Bronchoscopy has proved the most valuable diagnostic aid as yet offered and has led to the recognition of many obscure cases.^{58,94b}

Even with the numerous technical methods now available, it still rests with the internist to recognize the indications for their use. Probably many missed diagnoses were formerly the result of failure to think of bronchial tumors. Physicians are now, however, rapidly coming to realize that carcinoma of the lung must be included in their differential diagnosis when a patient in the "cancer age" presents himself complaining of loss of weight, cough, dyspnea, chest pain and blood-tinged sputum.^{26b,28,90}

The third and one of the most important arguments favoring the conclusion that the increase in lung cancers is apparent rather than real has to do with the changed attitude of the pathologist. With the advent of bacteriology, and especially the identification of the tubercle bacillus, a sound basis was available for the differentiation of infectious granulomata from lung tumors, and probably many old cases, formerly classed as tuberculous, were actually neoplastic. With our present knowledge of the characteristics of the two conditions, it is seldom that they could be confused on gross examination and never on the basis of microscopic study. Some difficulty may arise, however, when the lesions are coëxistent.

A further great step was made in the pathology of intrathoracic tumors with the recognition of the carcinomatous character of tumors formerly considered sarcomata of one kind or another. The gross characteristics of many primary bronchial growths, their tendency to form large mediastinal masses and to give rise to bizarre metastases was probably misleading. Likewise, the microscopic picture may, and often does, closely simulate that of a sarcoma. These were possibly the sources of error responsible for the astonishing conclusion reached by Rolleston and Trevor,⁷¹ in 1903, that sarcoma of the lung was commoner than carcinoma of the lungs and bronchi. In the light of our present knowledge, it is easy to identify as probably carcinoma, cases once reported as being sarcoma, such as those of Stevens⁸⁶ who considered carcinoma of the lung rarer and sarcoma commoner than was thought even at that time (1912). Adler¹ referred, in 1912, to the tendency of lung cancers to assume a sarcomatous form, while in 1926 Barnard,⁵ after studying the nature of "oat-celled sarcoma" of the mediastinum, concluded, on the basis of both gross and microscopic appearance, that these were actually bronchial carcinomata. He observed 12 cases of oat-cell tumor, all of which showed, in addition, areas composed of cells which were indistinguishable from those of an epithelial type. More recently Boyd,¹⁰ using the special silver stains of Hortega (Laidlaw's modification), satisfied himself as to the epithelial nature of these cells largely on the basis of the reticular arrangement. Duguid¹⁹ found many of the cases he reviewed had previously

been classed as lymphosarcomata. Though Weller^{94b} found a decrease in the incidence of sarcoma of the lungs concomitant with the increase in cancer, the number of sarcomata was too small to explain alone the increasing incidence of the epithelial growths. Frequent emphasis is laid upon the necessity of cutting numerous histologic sections from these sarcoma-like tumors,⁵ thus greatly increasing the chances of establishing indubitably the epithelial character of the tumor. Similarly, it has been observed⁸² that if a sufficiently diligent search is made in bronchial cancers of a well-differentiated cell type, areas of tumor composed of small, anaplastic, sarcoma-like cells will be found in almost all of them.

The dictum of Virchow and of Lubarsch that organs to which tumors were prone to metastasize were seldom the sites of primary growths, may have had considerable influence on the older pathologists, especially since the lungs were considered a typical example of an organ in which secondary tumors were common and primary malignancy correspondingly rare.

Though some authors consider it unsafe to say whether the increase in lung tumors is real or apparent,³³ others suggest that the latter is actually the case.^{6,19,50,72,82,94b} One of the strongest arguments favoring the conclusion that the increase is real, at least in part, is to be found in the reports of increased incidence coming from institutions which have been under the same supervision and have required the same standards of diagnosis for a number of years. An increase under such conditions has been reported by Rosahn,⁷² Weller,^{94b} Barron,⁶ Klotz,⁵⁰ Simpson,⁸² Duguid,¹⁹ Hunt⁴³ and many others, and forms, in part, the basis of their belief in the reality of the increase. The majority of these workers also believe that the arguments offered in explanation of the change being purely apparent are not sufficiently convincing to allow any final conclusions in that regard.

Statistics have been avoided, as the Reviewer is inclined to agree with the somewhat pessimistic opinion of Wells⁹⁵ as to their value. Their significance is further questioned when we find, as pointed out by Frissell and Knox,³¹ that Rosahn and Fried, using the same statistical material, came to opposite conclusions. Similarly, Kikuth⁴⁷ and Breckwoldt,¹¹ using the same and analogous material, also came to opposite decisions, as has been previously mentioned by Bonser.^{9a} Likewise, Passey and Holmes,⁶³ in reviewing the same material as Duguid,¹⁹ were unable to support the original conclusion that a real increase in the incidence of lung cancer had occurred.

It would appear, however, that much of the increase in bronchial carcinoma is apparent. How much of the increase is real will probably never be known, the world never having been in the state of a pathologist's Utopia where necropsy routinely follows death. Similarly, the true present-day incidence is uncertain, but nevertheless the condition must be considered sufficiently common and important to warrant the attention it has been shown.

Anatomic Varieties. At one time it was customary to differentiate between bronchial cancer and cancer of the lung parenchyma.^{39,69} This distinction can, however, for all practical purposes be discarded in favor of the modern view that they are one and the same. Indeed, Weller^{94a} required, in order to consider a case proven, good evidence of

bronchial origin in addition to other stipulations. Simpson⁸² points out that the condition cannot be diagnosed with certainty macroscopically. This is particularly true as regards the diffuse form to be referred to below. But when it has been established that an intrathoracic tumor exists, carcinoma of the lung must be differentiated from sarcomata, pleural tumors, carcinoma of the esophagus extending to involve the lungs, metastases from inconspicuous primary growths and inflammatory lesions.⁸²

Gross Anatomy. The gross appearance of bronchial carcinomata is extremely variable and yields little information as to the cell type to be found microscopically; hence a gross classification is highly unsatisfactory.⁴⁴ It is usual, however, to group them macroscopically as: 1, Infiltrating hilar; 2, nodular, single or multiple; and 3, diffuse. Such a grouping as this, suggested by Fishberg^{26b} and Weller,^{94b} and indeed adopted by most pathologists, is considered as unsound by Fried,^{29d} who records several cases to support this point. Fried considers that nearly all these carcinomata originate in close relationship to the hilum. He further doubts that any purpose is served by separating the diffuse and nodular forms, considering these to be mutually transposable. Despite this criticism some form of general gross grouping is desirable and useful.

The hilar infiltrating form is by far the commonest, and according to Weller^{94b} probably constitutes about 90% of all bronchial growths, though Frissell and Knox³¹ classified only 49% of their cases as such. Tumors of this type tend to form masses about the bronchi, usually at the root of the lung, with stenosis and ulceration of the lumina, and to extend peripherally around the blood-vessels, bronchi and over the pleura so as eventually to involve the major portion of a lobe or lung. It is this form that frequently gives rise to massive involvement of the peribronchial and mediastinal lymph nodes, which may attain an enormous size, while the primary growth may remain comparatively small.^{82,94b} The consistency of these hilar infiltrating growths is highly variable, depending largely, as is true of carcinomata elsewhere, on the cellularity of the growth, the density of the stroma and the extent of necrotic changes within the tumor. Frequently, hilar tumors are encountered with stenosis but no ulceration of the bronchus, and these often prove to be of a mucoid nature both in their gross and microscopic appearance.^{1,63,82}

The nodular form of primary lesion is comparatively rare. Usually this takes the form of multiple small circumscribed masses scattered through the lung parenchyma, varying from the size of a pinhead to that of a bean or larger and tending to coalesce in the advanced stages. It is frequently difficult or impossible to demonstrate any gross relationship of the tumor to bronchi. Thus there arises considerable difficulty in ruling out multiple metastases from an obscure primary growth. This is particularly true when the nodules are scattered uniformly throughout both lungs, rather than being confined to one portion of a lobe or lung. The multiplicity of nodules of fairly uniform size has led many to consider this as evidence of a multicentric origin.³⁷ A rarer form of the nodular type is the single, peripherally located growth described by Adler.¹ These are exceedingly rare but the

Reviewer has observed 1 such case. It is probable that these arise from the peripheral rather than hilar bronchi.

The *diffuse form* is also comparatively rare and, indeed, doubt has been expressed by some as to its actual existence, considering it merely a variation of the usual picture and not an entity in itself.^{29d} Here the gross appearance of the lung may closely simulate a pneumonic consolidation or interstitial fibrosis and the true nature of the process may not be recognized until microscopic study is carried out. Even then, all other possible sources must be excluded before one concludes that the tumor originated within the pulmonary tissues. Frequently these growths prove to be composed of cuboidal or cylindrical cells growing in a papillary adenomatous manner and lining the air spaces. This is the picture usually referred to when a pulmonary tumor is said to have had its origin in the lining cells of the alveolar spaces. Two such cases have been observed by the Reviewer. In one of these, the involved lung showed nothing in the gross other than collapse associated with a massive serous pleural effusion. In the second case, the appearance of the lung was typical of a chronic organizing pneumonia. It is of considerable interest that in both these cases a correct clinical diagnosis was made but could not be confirmed at autopsy until examination of microscopic sections revealed the diffuse malignant processes.

The secondary effects produced by a bronchial tumor are often extensive and may at times be confusing. Most of these are the result of interference with respiratory function, obstruction to the drainage of bronchial secretions and infection. These factors may lead to atelectasis, fibrosis, bronchiectasis, lung abscess, empyema, pneumonia and occasionally emphysema.^{26b, 29d, 94b} Often the symptoms resulting from these changes dominate the clinical picture.

Histogenesis. A histogenetic grouping of pulmonary tumors is even less satisfactory than a gross classification. This is due in part to the infrequency with which extremely early growths are encountered where their origin can be traced, and in part due to the inconstant histologic picture presented by the growths. Despite this, histogenesis is used by some as a basis for classification.²⁴

The epithelial elements of the lung from which carcinomata might arise consist of the bronchial mucosa and glands and the alveolar lining cells.⁶⁰ The bronchial mucosa is composed of the superficial cylindrical cells (which are mostly ciliated, goblet cells occurring only at intervals), an intermediate layer of replacement cells and the basal formative cells.⁶³ The bronchial mucous glands and their ducts are lined by cylindrical, non-ciliated, mucous and seromucous secreting cells. Passing down the bronchial ramifications to the terminal bronchioles, the lining epithelium becomes lower and lower, cilia and goblet cells disappear, until finally in the respiratory bronchioles it is composed of a single layer of low cuboidal or flattened cells.^{60, 63} A further transition occurs in the alveoli where the lining cells are of a flattened type. The peculiar activities of these cells have led many^{29b, 60} to doubt their epithelial character. Recently, however, on the basis of animal experimentation, Gazayerli³³ concluded that the normal lining consists of flattened, nucleated, epithelial cells and, in addition, scattered cuboidal cells of the reticulo-endothelial system with a phagocytic function (septal cells).

The difficulty in classifying pulmonary cancers in relation to these cell types arises from the fact that there is usually little resemblance between the tumor cells and normal pulmonary structures, and thus a histologic connection is difficult to establish. The greatest difficulties are encountered in the undifferentiated small-cell carcinomata and the completely differentiated epidermoid tumors with pearl formation. Furthermore, many growths show pleomorphic tendencies, and adenomatous, epidermoid and sarcoma-like areas may be found in the same tumor or even in the same section.^{5,50,58}

Actually, the ability of the alveolar lining cells to give rise to tumors is extremely doubtful and denied entirely by some, though Adler¹ considered a case reported by Marchand⁵⁹ to be conclusive evidence that growths may occasionally arise from this source. The reader may be referred to Fried's excellent discussion of this phase of the problem. In this connection, one of the most striking cases is that reported by Gray and Cordonnier,³⁷ who accidentally discovered in the course of routine microscopic study three separate minute cancer masses in lungs from the same case. Two of these had the appearance of arising from the epithelium of the ductus alveolaris, while the third resembled an early lymphatic metastasis. Recently, Sweany⁸⁷ described in detail a diffuse carcinoma of the lung to which he referred as a "so-called alveolar carcinoma." In this case the author suggested an origin from the epithelium between the lower respiratory bronchioles and the alveoli. Fried,^{29d} believing that all growths originate from the bronchial basal or germinal cells, emphasizes the futility of a histogenetic classification.

Histology. On the basis of the foregoing discussion, it is evident that both gross and histogenetic classifications are not completely satisfactory. The only remaining possibility is to classify bronchial carcinoma according to the histologic picture. This has frequently been done and has proved by far the most satisfactory grouping. The multiplicity of cell types has naturally resulted in some confusion and has encouraged somewhat lengthy and often unwieldy classifications. Thus, Shennan⁸⁰ recognized six histologic groups with severe subdivisions, and Fried^{29d} described five types. Actually it would appear that all carcinomata of the lung could be grouped as either undifferentiated, cylindrical cell, or epidermoid cell.

The true incidence of these various types is difficult to determine. In 23 cases recorded by Boyd,¹⁰ 17 could be classed as undifferentiated (anaplastic 13, medullary 4), 5 as epidermoid and only 1 as cylindrical cell (adenocarcinoma). Simpson,⁸² Bonser,^{9a,b} Frissell and Knox³¹ and others have also found the anaplastic type the commonest. But Weller^{94b} found 25 of his cases to be epidermoid, 20 cylindrical and 10 polymorphous, and Brines and Kenning's figures¹² agree with these very closely. On the other hand, Barron,⁶ Moise⁶³ and others have encountered the cylindrical cell growths most frequently. A review of 52 cases in the Department of Pathology of the University of Toronto reveals that undifferentiated growths occurred in 26 instances, cylindrical cell in 15 and epidermoid in 11 cases. The available statistics regarding this problem are not satisfactory for analysis^{94b} and inconsistencies such as those above are to be found throughout the literature. This is probably in part due to failure to recognize some of the undifferentiated tumors and in part due to different criteria for classification

being required by different pathologists.⁶³ Though Fischer-Wassels²⁷ estimated a quarter of all pulmonary growths were of the undifferentiated type, a general survey led the Reviewer to believe that about 40% of the growths took this form while approximately 30% of the reported cases fell into the cylindrical cell group and 30% into the group of epidermoid tumors.

The class of undifferentiated tumors comprises those anaplastic growths in which it is impossible to determine the type cell giving rise to the tumor. It would include the small spindle and oat-cell growths and probably many of the cases reported as medullary cancer and carcinoma simplex. Typically these tumors are composed of extremely cellular aggregations of small round or spindle-shaped cells with scanty cytoplasm and small, deeply staining nuclei.⁵ Ordinarily the stroma is delicate and has a relation to the cell masses characteristic of a carcinoma.¹⁰ Nearly always, if sufficiently diligent search is made, cells can be found differentiating out into either a cylindrical or squamous type and occasionally both may be seen in the same case.^{5,82} It is this type of growth which tends to produce the tremendous mediastinal masses and was formerly considered to be other than carcinomatous in nature.^{44,82} It is the finding of areas of greater differentiation in this type of tumor which lends weight to the contention that all bronchial growths spring from the germinal or basal layer of the bronchial mucosa, as has been suggested by Fried,^{29d} or from cells having a common ancestry.⁵⁰

The cylindrical cell carcinomata of the bronchi do not differ materially from those found elsewhere in the body. The more fully differentiated ones present the typical appearance of an adenocarcinoma, being composed of gland-like structures lined by one or more layers of cuboidal or cylindrical non-ciliated epithelium. Mucous secretion is common and this as well as the histologic resemblance to bronchial mucous glands gave rise to the theory that these tumors actually did originate in these glands. However, the fact that all degrees of undifferentiation are seen in these tumors,⁸² the presence of goblet cells in the bronchial lining,⁶⁰ and the common parentage of all the respiratory epithelium^{50,72} suggest that they might equally well have had their origin from the bronchial mucosa itself. Frequently, adenocarcinomata of the lung show a strong tendency to line the alveoli, using the normal structure as a supporting stroma. This has led some to suggest an alveolar origin for these growths. However, since a similar state of affairs is not uncommonly seen in secondary tumors in the lungs,⁵⁰ and since the nature of the alveolar lining cells is still in doubt, it is unsafe to draw any final conclusion.

The epidermoid cell type usually offers little difficulty in recognition, but some pathologists required the formation of pearls and typical intercellular bridges before admitting a case to this class.⁶³ It would seem more reasonable, however, to admit into this group the less completely differentiated types which resemble epidermoid carcinomata elsewhere in the body. Many of the older pathologists^{8,18} and others^{53,61} consider these tumors to be either of alveolar origin because of their flattened cells, or else derived from cell rests. Later, it was frequently suggested that they arose from metaplasia of the bronchial epithelium as this condition is not infrequently observed and especially in lungs

which are the seat of a malignant process.⁵⁸ Furthermore, it is this type of tumor which tends to occur in relation to chronic inflammatory conditions where metaplasia would be expected to occur. Examples of such tumors are those apparently originating in the walls of tuberculous and bronchiectatic cavities. The similarity in their essential character to the anaplastic tumors is to be seen in the areas of small round and spindle cells also encountered in these growths. Simpson⁸² points out that they may give rise to secondaries composed of "oat cells."

It would appear that the most satisfactory grouping is this simple classification based on the microscopic picture which is depicted graphically by Weller^{94c} as a Y, the stem representing the anaplastic group. The two arms of the Y represent differentiation toward the epidermoid or cylindrical cell types, the upper extremities of the arms indicating the highest degrees of differentiation. Brines and Kenning,¹² and also Samson⁷⁵ have successfully applied this method of grouping, though the former would further simplify it to only two types, differentiated and undifferentiated.

Metastases. The peculiar tendency of bronchial cancers to give rise to widespread metastases has long been recognized. Metastases were recorded in 280 of 374 cases collected by Adler.¹ Fried^{29d} observed metastases in all but 3 of his series of 47 cases. Similarly, all who have investigated the problem have been struck with the frequency and wide dissemination of the secondary deposits.

Almost every tissue and organ of the body has been recorded as the site of metastasis, but the highest incidence of extrathoracic deposits is in cervical lymph nodes, liver, abdominal lymph nodes, kidneys, suprarenals, bones, brain, pancreas, and thyroid, in about that order of frequency.^{6, 9a, 12, 29d, 31, 76} Turnbull and Worthington⁸⁹ found bronchial growths the commonest source for metastases in bones. The frequency of central nervous system and bone deposits varies widely in different reports, but discrepancies are probably dependent on the extent of the postmortem examinations.

The incidence of metastases to brain is of the greatest interest because of their high frequency and the widely accepted statement that cancer spreads *via* lymphatics. Fried and Buckley³⁰ were particularly interested in this problem and found 15 central nervous system metastases verified by operation or necropsy in 38 cases studied. They attributed this high incidence to a hematogenous spread and were able in all these cases to demonstrate invasion of blood-vessel walls and lumina by tumor. Boyd¹⁰ cites a similar experience. An analogy has been suggested between brain abscesses secondary to pulmonary suppuration and intracranial tumor deposits secondary to primary bronchial growths. As Fried³⁰ points out, the situation of the lung in the circulatory system would favor generalized hematogenous dissemination and the formation of metastases in the brain. Tumor emboli from primary sources other than the lungs would tend to be filtered out in these organs and thus fail to reach the brain or indeed the bones and other tissues having no close connection with the primary lesion. Moise⁶³ had previously suggested a hematogenous spread as the explanation of the widely disseminated metastases.

Although Boyd¹⁰ was unable to demonstrate any correlation between

the tendency of bronchial cancers to metastasize and the cell type or the degree of cell differentiation, Samson⁷⁶ arrived at a somewhat different decision in analyzing 100 carefully selected cases. These cases included 34 of his own, the remainder being selected from the literature on the basis of the completeness of the reports. By grouping the tumors as undifferentiated, squamous cell or adenocarcinomata and applying the "coefficient of association" he found the following characteristics: The adenocarcinomata showed a predilection for the central nervous system, adrenals, kidneys, both lungs and to some extent the liver and bones. This was explained on the basis of a hematogenous spread with involvement also of the thoracic and abdominal lymph nodes. The squamous-cell group was largely restricted to local extension with involvement of the bronchial lymph nodes only. The undifferentiated cell type showed extensive lymphogenous spread which was associated with involvement of pancreas, liver and spleen. This is in keeping with the observations of Fried³⁰ who failed to find any squamous or oat-cell tumors among 15 bronchial carcinomata with central nervous system metastases. The tendency of epidermoid bronchial tumors to extend by local and regional invasion has in the experience of the Reviewer been striking, with the exception of a single case of a well-differentiated epidermoid growth which had given rise to metastases in many organs, including the brain.

These facts have their clinical application, indicating as they do that the squamous-cell tumors offer the best prognosis where surgical intervention is undertaken.¹⁴ Moreover, it must be borne in mind that the presence of central nervous system metastases is apt to lead, in a large number of cases, to an incorrect diagnosis³⁰ and to subsequent treatment which at the best could be but palliative.

Etiology. Much has been written regarding the etiology of bronchial carcinomata and it is generally concluded that these neoplasms are subject to the same laws as govern the development of carcinomata elsewhere in the body.^{82, 94b}

Climate and Race. It would appear that climatic conditions have little if any effect on the incidence, though the disease is seen with greater frequency in Great Britain than in continental Europe.⁹³ Likewise, racial influences, although they have not been very extensively investigated, are apparently of little significance.⁶ However, it does appear that the white races are more susceptible than the colored.¹ Brines and Kenning,¹² at the Receiving Hospital, Detroit, Mich., observed that 50% of their cases were of Central European birth or extraction. Too few studies, however, have been made along these lines to permit any final conclusions.

Age. Cancer of the lung is essentially a disease of middle life. Though cases have been reported at both extremes of age,²⁴ all authors are agreed that the vast majority occur between the ages of 40 and 70, with the peak in incidence between 50 and 60 years.^{9a, 26b, 52, 94b}

Sex. The sex incidence of bronchial cancers is rather striking, since the disease is comparatively uncommon in females. The figures on the male to female ratio vary from 2 to 1 to 4 to 1.^{5, 9a, 26b, 29, 94b} In a series of cases studied by the Reviewer there were 49 males and only 5 females. A few observers have noted an even more extreme preponderance in males,¹⁰ but the majority of such reports deal with a

comparatively small number of cases. It has been suggested that much of the apparent increase in the disease has been due to its increased incidence among men. Careful analyses, however, such as were carried out by Bonser^{9b} fail to support this suggestion.

Occupation. This preponderantly male sex incidence has led many to search for some habit or occupation peculiar to the male which might be related to the origin of pulmonary growths.²⁰ Particular endeavor has been made to establish an occupational linkage.

Brockbank,¹³ in a series of 62 cases, found that 14.5% had pursued dusty trades while 29% had been exposed to fumes. Rosedale and McKay⁷³ found 75% of their cases had been exposed to dusts, and other similar instances are to be found in the literature.³² In marked contrast with these reports are the figures of Frissell and Knox,³¹ who found that only 3 of their 46 cases had been exposed to dusty atmospheres. The vast majority of those who have studied the problem feel that the results of efforts to establish an occupational correlation have, on the whole, been disappointing.^{9a,41,68} Sporadic reports of bronchial carcinomata occurring in particular occupations are constantly appearing in the literature, but a summation of these fails to disclose any abnormally altered incidence. An exception to this is to be found in the incidence of the much discussed lung tumors encountered among the miners at Joachimstal⁷⁰ and Schneeberg.^{77a,b} It is estimated that approximately 50 and 70% respectively of these miners, exposed for a sufficiently long time to the conditions of these mines, eventually die from bronchial carcinoma. The etiology of these tumors will be referred to later.

Naturally the occupations which have been most extensively investigated are those necessitating the inhalation of air contaminated by irritants, either physical or chemical.⁴ Much can be learned from the excellent report on the problem by Kennaway and Kennaway,⁴⁶ despite the fact that a large portion of their statistical data was obtained from death certificates. These investigators were unable to find any significant occupational incidence but observed that the highest incidence occurred among open air workers exposed to road dusts, with the exception of motor vehicle operators. Metal grinders and those exposed to coal gas, tar and tobacco dusts also showed a slightly greater incidence of lung cancers than the general population. Others, including Simpson,⁸² have also noted a high incidence among open air workers, but Bonser^{9b} was unable to support this finding, since the majority of her cases were indoor workers.

The observation has often been made that cancer of the lung is primarily a disease of the laboring classes.¹³ Though this may be true, the statement should be accepted only with reserve, since the majority of patients admitted to most of the large hospitals and institutions are of the laboring class, while the well-to-do patronize private hospitals and fail to come to autopsy.

Chronic Irritation. Approaching the problem from a different point of view, many investigators have made an equally exhaustive search for specific causes of bronchogenic cancers. Though none has been satisfactorily proven, it now appears highly probably that chronic irritation of the respiratory tract is of the greatest possible significance.¹² The irritants that have been incriminated include gross acute trauma, bacterial, physical and chemical agents.

Trauma. This is in all likelihood of no significance.^{1,52} Reports of cases of bronchial carcinoma apparently developing after an injury to the chest are scattered throughout the literature, but the majority are inconclusive. The most convincing is that recorded by Wells and Cannon.⁹⁶ In this particular case, the injury was immediately followed by the development of subcutaneous emphysema and hemoptysis, indicating that damage to the pulmonary tissues had occurred. Roentgen ray and physical examination revealed no neoplasm at that time. Two years after the accident, death occurred from a primary pulmonary cancer situated peripherally in the lung immediately beneath the site of the injury. It is, of course, impossible, as Wells himself admits, to prove that a minute neoplasm did not exist prior to the occurrence of the trauma.

Infections. As regards the relation of bacterial infections to carcinoma of the lung, attention in recent years has centered largely in the possible influence of influenza. This was probably stimulated by the apparent increase in bronchial growths observed by some workers as corresponding with and following the epidemic of 1918-1920.^{6,63} Peculiar lesions suggesting precancerous changes have long been recognized as occurring in the lungs in association with inflammatory conditions.³⁸ These changes, following influenza, were well described by Winternitz in 1920.⁹⁹ They took the form of active epithelial proliferations which often advanced to such an extent as to resemble "an infiltrating malignant epithelial neoplasm." Winternitz⁹⁸ also observed very similar changes in the lungs of rabbits following the insufflation of dilute hydrochloric acid. Askanazy³ observed that squamous metaplasia in the bronchi was common in individuals dying from influenza. Clinical studies have failed, however, to show any convincing relationship between influenza and bronchial tumors.^{29d,47,82} Many writers have observed that the peak in the alleged increasing incidence of bronchial cancer was reached prior to 1918, and no undue increase in the incidence of the condition was recorded following the influenza epidemic of 1894.^{42,94b} Furthermore, relatively few patients suffering from carcinoma of the lung give an antecedent history of influenza, and doubt has also been expressed as to the ability of a single acute infection to initiate changes leading to the development of cancer.^{29d}

Among the chronic infective pulmonary lesions, tuberculosis has been accused most frequently of being one of the causative factors responsible for bronchial carcinoma. Cancer of the skin following lupus vulgaris is frequently pointed to as an analogous example.^{29a,65} Ewing,²⁴ in 1928, stated that tuberculosis was the chief etiologic factor, basing his conclusions on the apparently frequent coëxistence of the lesions as reported by some authors. Barron⁶ also considered tuberculosis as an important factor. Actually, tuberculosis is encountered not infrequently in association with bronchial growths, but it is doubtful if the association of tuberculosis is any commoner with carcinoma of the lung than with other diseases. Usually there is no evidence of anatomic relationship between the two processes and more often than not the tuberculous lesions are entirely inactive. In 139 cases studied by Simpson⁸² evidence of tuberculosis was found in only 47. In 6 of these the tuberculous process was active; in 7, healed nodules were found in the lungs; and in 34 there were only calcareous hilar and mediastinal

glands. Frissell and Knox³¹ observed tuberculous lesions in only 18.6% of their cases, while Sison and Monserrat,⁸³ in the Philippines, noted that the incidence of lung cancer was low while that of tuberculosis was high. Fried^{29d} found a lower incidence of malignancy among a group of tuberculous cases than in a similar group of non-tuberculous individuals. Similar experiences have been reported by Lubarsch,⁵⁶ while Lóizaga and Vivoli⁵⁵ encountered but 1 carcinoma of the lung in 2400 autopsies on tuberculous patients. Fishberg^{26a} suggests that the presence of a pulmonary neoplasm may by pressure activate an old tuberculous focus, but considers the association of the two conditions uncommon. Fried^{29c} has recently reported a series of 13 cases in which the lesions coëxisted. While tuberculosis cannot be considered a common etiologic factor, it would seem reasonable to agree that those carcinomata reported as arising in tuberculous cavities are probably the result of the chronic inflammatory changes and consequent metaplasia, but this does not imply any carcinogenic effect on the part of the tubercle bacillus itself.

Non-specific chronic inflammatory lesions of the lungs would appear to be of considerable importance as a predisposing factor. Thus squamous-cell growths arising in bronchiectatic cavities are not rare. Marron⁶ suggests that the bronchiectasis is more likely the result rather than the cause of the growth. Though this is certainly often true, it is not always so. The Reviewer has observed 1 case in which the tumor formed the walls of a bronchiectatic cavity in an individual who had suffered from bilateral bronchiectasis for at least 15 years. Frequently, it is possible to elicit a history of chronic bronchitis, recurring attacks of pneumonia or other low-grade inflammatory pulmonary condition in patients suffering from a bronchial growth.^{29d,43,82} It is even commoner to find gross and microscopic evidence of chronic pulmonary inflammation at autopsy.^{50,63} Caution, of course, must be exercised in expressing an opinion as to whether or not these chronic inflammatory changes antedated the development of the neoplasm. Gray and Cordonnier's case³⁷ is an excellent example of an extremely early growth in a chronically diseased lung. These chronic and apparently non-specific conditions are frequently the sequelæ to previous acute events and probably of greater significance than the original acute irritation.⁵⁰

The relationship between chronic inflammation of the lungs and carcinoma is probably dependent upon injury to the epithelial elements with regeneration and often metaplasia. That metaplasia does occur in association with many conditions, including tuberculosis, bronchiectasis, fibrosing pneumonias, collapse of the lung and chronic bronchitis has frequently been pointed out.^{29d,50,94b} Geschickter and Denison³⁵ and von Glahn⁹¹ noted that squamous-cell tumors of the lung were commoner in the upper age group and it is in the aged that metaplastic changes are most often observed.⁵⁰ The bronchiectasis with metaplasia which has frequently been observed in laboratory rats and on occasion erroneously described as a squamous-cell tumor cannot be considered comparable to the disease in man, since it has a totally different etiologic background.⁶⁹

Syphilis of the lung has occasionally been recorded as being associated with bronchial cancer⁸² but is rare and probably bears no causal relationship other than that of a chronic irritant. Even rarer is the asso-

ciation of pulmonary cancer and parasites, even those parasites notorious for their ability to initiate neoplastic lesions elsewhere.^{29d} Eggers²³ quotes 1 case reported by Babes of bronchogenic cancer associated with trichinosis.

Chemical and Physical Agents. The alleged increase in the incidence of lung tumors has resulted in an analysis of the habits of modern civilization in the hope of discovering some predisposing factors. Thus, smoking of tobacco, exposure to dust from tarred roads and the inhalation of fumes from gasoline engines have all been incriminated. McNally⁶¹ suggested that nicotine, phenol bodies, pyridine bases and ammonia, contained in cigarette smoke, were irritants which could account for "cigarette cough," chronic bronchitis, leukoplakia and the recorded increase in cancer of the lung. Hoffman,⁴⁰ on the basis of elaborate and confusing statistics, concluded that smoking habits unquestionably increase the liability to cancer of the mouth, esophagus, larynx and the lungs. Hoffman adds the astounding statement that non-smokers are subjected to the same dangers owing to air pollution by smokers. However, it is more than likely that smoking is of absolutely no importance. The available statistics are open to far too many objections to bear any weight. Bronchial cancer is common among non-smokers, and indeed Brockbank¹³ found but 14.5% of his cases heavy smokers, while 21% were non-smokers. Furthermore, if smoking were a factor of any importance it is probable that a striking change in sex incidence would have been observed owing to the rapidly growing prevalence of the habit among modern women.^{94b}

The development of tarred roads led to much speculation as to a possible etiologic relationship. Some weight is lent to this idea by such observations as those of Kennaway and Kennaway,⁴⁶ who noted an increased incidence of cancer of the lung among open air workers exposed to road dusts. It seems remarkable, however, that this observation did not apply to motor vehicle operators who surely suffer a similar exposure. Though a high incidence of lung tumors has been reported from regions where road tarring is not practised,¹⁰ Campbell¹⁵ does not consider this an argument against an etiologic relationship, stating that dust from such roads may be carried tremendous distances by the air currents. This cannot, however, be considered tenable in view of reports from communities¹⁰ where the injurious agents would have to be carried hundreds or even thousands of miles. Campbell¹⁵ found a high incidence of warts which underwent malignant changes in laboratory animals exposed to dusts from tarred roads, but no pulmonary neoplasms developed. Passey and Holmes,⁶³ carefully analyzing the problem, point out that the alleged increase in lung cancer in Great Britain appeared prior to the tarring of roads. They further suggest that if the time factor required to produce growths in animals, as demonstrated by Campbell, were applied to man, the effect of road tarring should just now be making itself felt.

Fumes from gasoline engines and pollution of the air in industrial centers^{19,79} can be considered under the same category of etiologic agents as dusts from tarred roads. There is certainly no direct evidence to connect lung cancers with the first of these. Though a high incidence of carcinoma of the lung has been noted in some industrial centers where air pollution was great, an equally high incidence has

been observed in rural communities.¹⁰ It has also been noted that there is no undue occurrence of the disease among mechanics and garage workers who are constantly exposed to a polluted atmosphere.⁶⁸ Although Kimura,⁴⁸ in 1923, reported an adenoma of the lung in a rabbit and an adenocarcinoma of the lung in a guinea-pig following the insufflation of coal tar, Smith,⁸⁵ in 1928, was unable to produce pulmonary tumors in mice by exposing the animals to pitch fumes, products of an internal combustion engine, or by painting the skin with gasoline. Although Smith thus found nothing to support the theory that fumes from coal tar or gasoline were of importance in human cases of bronchial cancer, reports such as that of Kawahata⁴⁵ are most suggestive. This investigator observed 12 cases of the disease among employees tending furnaces for gas production, where the air contained several tar derivatives with unknown carcinogenic properties. Recently, Seelig and Benignus⁷⁹ found 8 adenocarcinomata of the lung in 100 mice exposed to coal soot, while only 1 tumor developed in their controls. It must be concluded, however, that the evidence incriminating inhaled tar products as a cause of cancer of the lung in human beings is as yet far from convincing.

The peculiarly high incidence of bronchial cancers seen among the miners at Schneeberg and Joachimstal, and previously referred to, has also led to speculation regarding the possible presence of a specific agent in the mine dusts. The dusts of both mines are radioactive and, in addition, contain bismuth, cobalt, nickel and arsenic. Analysis of lungs obtained at autopsy from miners at both these sources have proved entirely negative as to radioactivity and any significant chemical content. As pointed out by Pirchan,⁷⁰ these negative results do not rule out the possibility of a chemical factor, no trace remaining owing to its rapid removal. Arsenic has been suspected because of its known carcinogenic effects upon skin.⁵⁰ Schmorl^{77a} was impressed by the constant and marked pneumoconiosis found in association with the growths at Schneeberg, and he originally believed that physical irritation was the probable cause of the tumors. Later, he suggested that the radioactivity as well as the arsenic content of the dust might be additional factors.^{77b} Mice exposed to the mine dusts showed only negative results.⁷⁴ The Schneeberg mines are described as damp, infested with a variety of moulds and conducive to the development of chronic bronchial catarrh^{77b} which in itself might be of some importance. At Joachimstal, pneumoconiosis was not a prominent feature, as shown by Pirchan,⁷⁰ but the lungs of miners dying with pulmonary growths presented a picture otherwise morphologically identical with that described by Schmorl. Pirchan was inclined to consider the radioactivity of the mine dusts and air as the most probable specific agent. It is said that the incidence of carcinoma of the lung is decreasing at Schneeberg following the introduction of respirators,^{29d} which suggests that the factors responsible for the pneumoconiosis are also related to the production of the growths. On the other hand, respirators have been used at Joachimstal and the incidence of tumors remains high, while pneumoconiosis is uncommon.⁷⁰ This problem, though fascinating, is confusing in the extreme and can by no means be considered settled.

Silica has frequently been considered as a possible etiologic agent and

a number of cases of silicosis associated with carcinoma of the lung have been reported. However, it has been pointed out by Simpson⁸² and Passey,⁶⁸ and more recently, by Vorwald and Karr,⁹² that cancer of the lung is rare among South African gold miners, while silicosis is common. Indeed, the latter investigators found a slightly diminished incidence of the disease among silicotics as compared with the population at large. This failure to show an increased incidence is in accord with the earlier observations of Pancoast and Pendergrass,⁶⁷ Allen² and others. However, numerous cases where silicosis and cancer of the lung have co-existed are now to be found in the literature.^{17,22,25,32,36a,b,57,66} Dible¹⁷ and others believe there may be a direct relationship. Willis and Brutsaert⁹⁷ observed tumor-like structures surrounding the bronchi of several guinea-pigs from a series of animals exposed to silica for long periods of time. They concluded that these lesions were in all probability a hyperplastic response to the irritating silica. The Reviewer⁴⁹ reported recently an extremely high incidence of bronchogenic carcinoma in a small series of silicotics numbering 50, 9% of which showed primary epithelial malignancies of the lungs in addition to the lesions resulting from prolonged exposure to silica. It was, therefore, suggested that silica might in certain cases be a specific predisposing factor.

Ewing²⁴ suggested that pulmonary carcinoma might possibly arise from bronchial papillomata. This must indeed be rare as the incidence of benign epithelial bronchial growths is exceedingly low. In reviewing the literature up to 1935, reports of only 58 benign bronchial growths of all types were encountered, and only 18 of these were sufficiently well described to be classed as epithelial. The remainder was composed of tumors referred to as polypi, granulomata, chondromata, lipomata and so forth.

Heredity. A discussion on the etiology of cancer of the lung would not be complete without reference to hereditary factors which may prove to be of extreme importance. Though no hereditary factor has ever been satisfactorily demonstrated in carcinoma of the human lung,⁶ Slye⁸⁴ and others find an extremely strong hereditary predisposition in mice. By careful breeding, it is possible, as has been frequently demonstrated, to develop cancerous and non-cancerous strains. On the basis of such studies as have been made on tumors in identical twins, Lockhart-Mummery⁵⁴ concludes that the "intrinsic factor of hereditary susceptibility to tumour formation in human beings is of far greater importance than the extrinsic or environmental factor." Fischer-Wassels²⁷ also apparently believes this to be of considerable importance in relation to cancer of the lung in man, and suggests that the probable sequence of events in the development of such a tumor is hereditary predisposition, irritation, repair with excessive proliferation and finally malignancy, and one finds it difficult not to agree.

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HYGIENE AND PUBLIC HEALTH.

UNDER THE CHARGE OF

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CHANGING CONCEPTIONS OF SCARLET FEVER.

Severity. Pope,²² in 1926, using Chapin's material, reviewed the experience of Providence, R. I., in regard to scarlet fever in the years from 1865 to 1924. The death rate for children of ages from 2 to 4 had decreased in this interval from 691 to 28 per 100,000 (or to about 1/25 of the rate of 70 years ago) but the attack rate had not presented a corresponding decrease. The decrease in the number of deaths could not be attributed to a lower average prevalence nor to any changes in the population, but must have been due to the lessened severity of the disease. In 1886-88, 1 in every 5 cases died, while in 1923-24, only 1 of every 114 cases ended fatally.

In a recent (1933) publication, Woods³¹ has shown that a similar change has occurred in England and Wales. While the population of children exposed to risk has increased some 40%, the deaths from scarlet fever are less than 1/25 of the absolute number recorded 80 years ago. In the face of this decrease in the death toll, the disease has not diminished generally in prevalence. The decrease in the number of fatalities is due to the lessened severity of the disease.

These observations could be amplified and corroborated by a review of other reports, but the general facts are well established and appreciated. Although the decrease in the case fatality rate has been more rapid in some areas than in others, perhaps more marked in southern than in northern climes, and more apparent during endemic than during epidemic prevalence, it has become general throughout Europe and America. From a fearful and highly fatal malady scarlet fever has become a relatively mild and, in the vast majority of instances, an innocuous ailment.

That it will continue to exhibit its present mild character is open to question. To Thomas Sydenham, "*febris scarletina*" was a mild disease. By the end of the eighteenth century, a severe form was prevalent in England, for in Willan's reports on diseases in London in the years from 1796 to 1800, there are numerous references to the gravity of the scarlet fever at that time. Immediately after this period, the severity diminished. Bateman, writing of the disease of London in years from 1804 to 1816, frequently alludes to the mild type of scarlet fever. There is no question that a change occurred after 1830 and the disease became, as Creighton noted, "the leading cause of death among the infectious diseases of childhood." Apparently it remained so in England and in this country until the middle of the nineteenth century, when the decline in mortality that has been noted began and has continued to the present time. This history is a warning against optimism until the causes of the decrease can be defined and explained.

Pathogenesis. With the advent of the bacteriologic era it was confidently expected that the disease "scarlet fever" would be found to be due to a specific microbial incitant, just as were diphtheria, typhoid, tuberculosis and other common infectious disease. After 50 years of research, the true nature of the pathogenesis of the disease syndrome has finally become apparent.

The etiologic relationship of streptococci was suspected very early, but attempts to separate those types which were capable of causing scarlet fever from those which were not, by means of cultural and serologic procedure, were only partially successful. It became evident that they belonged to the "hemolytic" streptococci and that they possessed some degree of antigenic relationship. The nature of the essential biologic activity which distinguished them remained undiscovered until some 15 years ago.

At this time, as a result of the observations and experiments of Schultz and Charlton, Mair, Dochez, and the Dicks, it became evident that the peculiar biologic activity which distinguished the hemolytic streptococci which caused scarlet fever was their ability to produce a particular toxin, called Dick toxin, or, more properly, erythrogenic toxin, erythrotoxin, or simply rash-producing toxin. It was demonstrated that the injection of bacteria-free filtrates of broth cultures of hemolytic streptococci containing this erythrotoxin into susceptible human beings reproduced cardinal symptoms of scarlet fever, except the sore throat; namely, fever, malaise, nausea, vomiting, and a generalized scarlet rash. This afforded a rational interpretation of the pathogenesis. The sore throat is due to the primary localization of a strain of hemolytic streptococci in the throat with the resulting inflammatory reaction. The characteristic constitutional reaction is due to the toxic products peculiar to these organisms. The complications and ultimate outcome are determined by the ability of the organism to proliferate locally and to invade the tissues progressively. Resistance and recovery depend upon the development of at least two types of immunity: (a) ability to prevent the growth and progressive invasion of the microorganism, that is, antibacterial; and (b) ability to neutralize the toxic products, especially the erythrotoxin, that is, antitoxic immunity. To what extent the latter affects the former is not yet clear.

This conception of the pathogenesis of scarlet fever has now received general acceptance. It raises a pertinent question: Should scarlet fever be regarded as a separate and distinct disease or simply as one of the clinical patterns or syndromes resulting from infection with hemolytic streptococci? The answer will depend very largely on whether it can be demonstrated that hemolytic streptococci which cause scarlet fever form a separate and distinct group meriting some such appellation as "*Strep. hemolyticus* var. *scarlatinae*" or equivalent.

Identification of Scarlet Fever Streptococci. The question of the specificity of the scarlet fever streptococci is but a small part of the larger problem of the classification of streptococci in general and the correlation of types or subdivisions with the various conditions of health and disease in which they are found in man and animals. The present (1937) status of knowledge has been admirably reviewed by Sherman.²³ Attention here will be limited to those streptococci which produce characteristic beta-type hemolysis in blood agar.

In the previous discussion, it was pointed out that the significant biologic activity which distinguished the hemolytic streptococci recovered from cases of scarlet fever was their ability to produce, under specified conditions of culture, the characteristic erythrogenic toxin. Effort has been made to use this quality as a means of identification. It has become evident, however (Kirkbride and Wheeler,¹⁵ Eagles,^{7b} Smith,^{24b} McLachlan,^{20a} *et al.*), that the ability to produce erythrogenic toxin is a function not peculiar to strains of hemolytic streptococci from scarlet fever alone, but possessed not infrequently by non-scarlatinal strains. Neither on the basis of the quality nor quantity of erythrogenic toxin produced can a sharp distinction be made.

Researches upon the serologic identification of hemolytic streptococci, although discouraging for a long time, recently have been proved to be of considerable value. It will be recalled that up to 1930 there were two schools of thought. From the work of one group, Dochez, Avery and Lancefield,⁶ Bliss,³ Eagles,^{7a} Gordon,⁹ *et al.*, it appeared that most strains of hemolytic streptococci—if not all—which caused scarlet fever, could be identified by three or four properly prepared type-agglutinating sera, and that they formed a group serologically distinct from non-scarlatinal strains. To the other group, working more recently, Griffith,¹¹ Smith,^{24a} James,¹⁴ and McLachlan and Mackie,²¹ it seemed that the situation was not so simple. Although certain predominant serologic types could be demonstrated among scarlatinal strains, similar types could be recovered from non-scarlatinal sources. Summarizing in 1932, the late Sir Frederick Andrewes² concluded that no one serologic form can be credited with the causation of scarlet fever, though three or four recognizable serologic types, namely, Griffith's four major types, I, II, III and IV, seemed to be exceptionally commonly found in cases of the disease. To him it seemed that "the more one studies hemolytic streptococci the more strongly is the impression gained that they are in a state of constant flux in which it is difficult to find any firm foundation for a permanent systematic classification."

However, even while these pessimistic views were being written, the researches of Lancefield¹⁶ upon the antigenic composition of the streptococci were paving the way for the firm foundation of which Andrewes speaks. By means of a precipitin reaction, based upon the presence in

these organisms of a group specific polysaccharide, the "C" substance, it was found that the hemolytic streptococci could be divided into broad serologic groups which correlated significantly with previous knowledge of host relationships and pathogenicity. In particular, nearly all of the strains of hemolytic streptococci which are important in human pathology, fall into one group: Lancefield's Group A (Swift, Lancefield and Goodner,²⁷ Hare,¹² Davis and Guzdar,⁵ Lancefield and Hare,¹⁷ Hare and Maxtell,¹³ Colebrook, Maxtell and Johns⁴).

Having established this broad group, it is possible to subdivide it into types by means of a precipitin test based upon extracts of the type-specific protein, the "M" substance contained in streptococci, or by means of agglutination. Independently, Griffith,^{11b} by means of a slide agglutination, had established 27 types of *Strep. pyogenes* and stated that more than 30 such types exist. All but two or three of Griffith's types have been found to belong in Lancefield's Group A. There was thus afforded the basis for the serologic identification of the principal pathogenic hemolytic streptococci and their subdivision into types.

On the basis of experience up to the present time, certain types, 1, 2, 3, 4, 8, 10 (N. Y. 5), 11, 12, 23, have been found fairly commonly in scarlet fever; Types 5, 6, 13, 15, 19, 22, 26 and 27, less often. It is equally notable that these same types, and those remaining, have been found in non-scarlatinal conditions, such as tonsillitis, septic sore throat, otitis, mastoiditis, septicemia, puerperal sepsis, erysipelas, as well as occasionally upon normal human skin and mucous membranes. In other words, *by serologic technique the types of hemolytic streptococci which cause scarlet fever can be identified, but they cannot, by this means alone, be differentiated sharply from the other types in Lancefield's Group A which have been recovered from non-scarlatinal conditions.*

Production and Purification of Erythroxin and the Dick Reaction. One of the most valuable contributions of the Dicks was the development of the skin test which bears their name. It is not intended to review here the extensive literature which has appeared supporting the view that the principal hypothesis upon which the test rests is correct. Experience has shown that anomalies occur as with other similar tests (McGibbon,¹⁹ Fraser^{8d}) and certain limitations to interpretation which were not at first appreciated have become apparent.

Two important sources of error have been demonstrated: (a) the confusion caused by allergic reactions to other constituents of the test material, and (b) qualitative differences in the erythroxin produced by some strains of streptococci.

Although there has been some difference of opinion as to the frequency of "pseudo-reactions" due to allergy, and the necessity, therefore, for a simultaneous control test, recent work has emphasized that this source of error cannot be ignored.

As a result of the researches of Ando, Kurauchi and Nishimura,¹ Toyoda and Fugati,²⁸ Green,¹⁰ and Veldee,³⁰ it has been found that crude filtrates produced according to the Dick method contain at least two substances capable of invoking skin reactions: (a) The first is contained in an alcohol-insoluble fraction. It is heat-labile, that is, completely inactivated by heating for 30 minutes at 100° C. It invokes the Dick test reaction of susceptibility, combines readily with antitoxin and produces the symptoms of scarlet fever (except sore throat) when

injected in a sufficiently large dose in a Dick-positive child. This fraction evidently contains, in a considerable degree of purity, the essential erythrogenic toxin. (b) The second fraction is both alcohol- and acetic acid-insoluble. It is heat-stable, that is, boiling for 3 hours is required to destroy it. It possesses no combining power with antitoxin. It produced both local and constitutional reactions (but which are not typical of scarlet fever) when injected in sufficiently large doses, particularly in an adult. It is apparently identical with the nucleoprotein obtained by the extraction of the washed bacteria themselves, and the skin reaction resulting from the injection of this fraction is a manifestation of sensitization to this bacterial protein without relation to susceptibility to scarlet fever.

Veldee³⁰ (1937) notes that the coëxistence of these two fractions in the crude toxin should cause no surprise in view of our more extensive knowledge of the reactions induced by diphtheria toxin where an exactly parallel situation exists. Susceptibility to the true toxins in either disease occurs when the circulating antitoxin falls sufficiently low; whereas reaction to the heat-stable bacterial protein is dependent upon sensitization to this protein brought about by actual contact with specific protein. Hence we find that disease susceptibility (as measured by the Dick or Schick tests) decreases with age and extent of exposure; whereas sensitivity to nucleoprotein increases with age and extent of exposure. Not infrequently, reaction to both factors exists in the same individual.

Concerning the second source of error, although the erythrotoxin produced by most strains of scarlet fever streptococci is essentially similar, some degree of heterogeneity exists (Trask and Blake²⁹). To cover the range of variation, the Dicks require that the pooled products of four selected strains be used in the manufacture of toxin and antitoxin. The scarlet fever antitoxin in routine use produced under the Dick patents neutralizes the toxins used in the Dick test, but fails to neutralize the toxins of about 10% of the strains isolated from patients (Fraser³¹). When exposure to such strains occurs, one might expect even a Dick-negative person to develop scarlet fever.

With these qualifications, the Dick test is a reliable indication of the level of "anti-erythrotoxin" in the individual's tissues. It has not yet been proved, however, that a negative Dick test necessarily implies an ability to resist infection with hemolytic streptococci of Lancefield's Group A.

Relation of Scarlet Fever to Other Infections With Group A Hemolytic Streptococci. That scarlet fever streptococci might cause infections of the throat without a rash had long been suspected and was definitely established by Stevens and Dochez.²⁶ They observed that such infections occurred among persons who had negative Dick reactions, implying again that immunity against the erythrotoxin does not necessarily imply protection against the angina. Studies of the frequency of negative Dick reactions in relation to age and a history of attack have suggested that a considerable proportion of persons, perhaps 4 out of every 5, gain their antitoxic immunity (Dick-negative reaction) without having had a recognizable clinical attack of fever with rash. Such observations would indicate that infections with

hemolytic streptococci capable of causing scarlet fever, occur far more frequently without the rash than they do with it.

In this connection, a recent study by Stebbins, Ingraham and Reed²⁵ of the records of 1529 cases of streptococcus infection occurring in 7 milk-borne epidemics in New York State during the period 1934-36 is most interesting. The source of contamination of the milk supply in 6 out of 7 outbreaks was shown to be a cow suffering from an acute mastitis caused by a hemolytic streptococcus belonging to Group A. Three of these epidemics were classified as scarlet fever and 4 as septic sore throat. The clinical manifestations of cases observed in the various outbreaks were strikingly similar, with the exception of the presence or absence of a characteristic scarlet fever rash and desquamation. In the 3 epidemics classified as scarlet fever, a typical scarlet fever rash was observed in 60% of the cases; 40% had no rash. The character and frequency of complications were practically the same in the septic sore throat cases as in the scarlet fever cases. A previous history of scarlet fever had no influence on the frequency of infection with either clinical type of infection, but was associated with a lower incidence of rash in the scarlet fever cases. Dick tests done after recovery indicated that the proportion of persons who had become negative as a result of their illness was greater among those who had had scarlet fever than among those who had had septic sore throat.

The implications of this study may be extended to other human infections with hemolytic streptococci of Group A, such as otitis, mastoiditis, puerperal sepsis, wounds and burns (Longcope¹⁸). Whether or not the infection is accompanied by a *scarlet rash* will depend upon the balance between two factors: (a) the ability of the invading strain to produce a sufficient quantity of erythrotoxin under the conditions of growth in the tissues; and (b) the ability of the host to produce sufficient quantities of anti-erythrotoxin to neutralize this toxin. If the rash becomes manifest or if the case is associated with others which show a rash, it is classified as "scarlet fever." If no rash becomes apparent, it is an "infection with hemolytic streptococci." Whether the rash is of importance in prognosis or only in diagnosis is not yet clear, as the ultimate outcome of the infection depends upon the ability of the organism progressively to invade the tissues. To what extent production of erythrotoxin facilitates this invasion is unknown.

Public Health Implications. From these considerations, it appears that neither from the point of view of specificity of the etiologic organisms nor from the point of view of clinical manifestations is scarlet fever a distinct disease. Just as the hemolytic streptococci which cause it merge into the other streptococci of Lancefield Group A, so the classical disease syndrome merges into those of related infections caused by this group. Accordingly, scarlet fever should be regarded simply as a clinical manifestation of infection with one of the types of the Group A streptococci.

If this view be adopted, then it follows logically that any program of prevention should deal with this whole group of infections and not simply with those which show a rash. This applies to efforts to develop a satisfactory artificial immunity as well as efforts to control by quarantine and isolation.

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THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

OCTOBER, 1938

ORIGINAL ARTICLES.

THE MENTAL SYMPTOMS OF PELLAGRA.

THEIR RELIEF WITH NICOTINIC ACID.*†

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MENTAL changes as a part of the pellagra syndrome have been recognized by many physicians, and in areas where the disease is endemic these symptoms are so common and so striking that they have become associated with pellagra even by the lay observer. Various abnormal psychic states have been described in medical literature on pellagra, and some writers have thought that one or another psychosis was typical of this disease.

Subclinical pellagrins are noted for the multiplicity of their complaints, among which are many that are usually classified as neurasthenic. The most common of these symptoms are fatigue, insomnia, anorexia, vertigo, burning sensations in various parts of the body, numbness, palpitation, nervousness, a feeling of unrest and anxiety, headache, forgetfulness, apprehension and distractibility. The conduct of the pellagrin may be normal; but he feels incapable of mental or physical effort, even though he may be ambulatory.

* Read as part of a presentation before the Society of Physiological Neurology, Atlantic City, May 1, 1938.

† This study was made possible by a grant from the Rockefeller Foundation, supplemented by grants from Ciba Pharmaceutical Products, Inc. for the study of coramine, from the S. M. A. Corporation for the preventive studies, and from Mead Johnson & Co. for the nutritional studies in children. The latter two studies are still in progress.

The noticeable and more serious mental signs of pellagra manifest themselves in various types of psychoses. The most common is perhaps that in which loss of memory, disorientation, confusion and confabulation are predominant. There are also types in which excitement, mania, depression and delirium may occur. In our experience, a paranoid condition is common in pellagrins. These patients, acting on their paranoid delusions, are more active than are other pellagrins with psychoses. We claim no priority in observing the difference in the mental symptoms in various patients, for many writers on the subject have attempted to classify the neuroses and psychoses of the disease. Niles⁹ and Wood²⁰ noted the paranoid trend in pellagrins suffering from psychiatric difficulties.¹ They recorded particularly the pellagrin's fear of and antipathy toward relatives, with delusions of persecution. There is not space for an involved discussion of the classification of the mental signs of pellagra. The case reports which follow may satisfy those interested in the classification of psychoses. Numerous definitions have been fitted to the term "neurosis," and it has been used in the past in many of the writings on pellagra. Although objections will probably arise to the use of this term, it will be used (for want of a better one) in the present report to describe the prodromal complaints listed above. In a language which is not noted for its preciseness, it will do for the purpose at hand. The same symptoms, of course, occur in association with many other diseases, but in the present study they will be considered as the prodromal part of the pellagra syndrome. The treatment described below is not advocated for any mental disability except for that associated with pellagra.

In September, 1937, Elvehjem, Madden, Strong and Woolley¹ reported that nicotinic acid cures blacktongue in dogs, a canine disease which is believed to be analogous to pellagra in human beings.^{3,7,8,13,19,21} Since all food substances which have been found to be curative and preventive for canine blacktongue have likewise proved beneficial in the treatment and prevention of human pellagra, several investigators were encouraged to determine the effect of nicotinic acid on this disease. Spies, Cooper and Blankenhorn¹⁶ have shown that pellagrins respond dramatically to the administration of this drug. Beneficial results have also been observed independently by other investigators in the field.^{2,5,6,10,11,18} Spies, Sasaki and Gross¹⁷ and Spies, Bean and Stone¹⁴ have mentioned briefly that the early and late mental symptoms of pellagrins in relapse and of subclinical pellagrins are relieved by nicotinic acid. In a larger series of cases it has been possible to institute control measures in order to study more specifically the mental symptoms of pellagrins in relapse and their response to nicotinic acid. Related studies on subclinical and mild cases have also been made. It is our purpose in the present paper to record some specific observations on the

treatment of the psychoses and "neuroses" of pellagra with nicotinic acid and the diethyl amide of nicotinic acid.*

Material and Methods. The present study includes the following groups: 60 pellagrins with acute psychoses and other manifestations of pellagra as shown in the table; 15 other pellagrins with no mental symptoms but with characteristic dermatitis, glossitis, stomatitis and gastro-intestinal involvement; 424 subclinical and mild pellagrins who have been subject to one or two annual recurrences of the disease; 26 patients with psychoses of other types; and 129 pellagrins who had had one or two recurrences of their "neurotic" symptoms each "pellagra season" since the onset of their disease.

A. Pellagrins With Acute Psychoses. A total of 60 pellagrins with acute psychoses was studied at the Hillman Hospital, Birmingham, and at the General Hospital, Cincinnati. All of these patients had typical pellagra and were admitted to these hospitals between September 15, 1937, and June 1, 1938. A summary of some of the more common symptoms and physical signs is given below:

TABLE 1.—SUMMARY OF 60 CASES WITH ACUTE PSYCHOSES.

Male, 19; female, 41. White, 29; colored, 31.

Symptomatology.

Mental symptoms	60	Porphyrinuria† (of 40 tested)	40
Weight loss	60	Diarrhea	33
Stomatitis	56	Tachycardia	32
Glossitis	56	Peripheral neuritis	21
Dermatitis	55	Vomiting	19

Type of Pellagra.

Endemic, 35.

"Alcoholic," 6.

Secondary to organic disease, such as gastro-intestinal diseases, 19.

Method of Control.

Water and glucose by mouth	21
Only water by mouth	20
Diet low in antipellagic factor	10
Hospital diet	9

* The nicotinic acid used in treating the pellagrins with spontaneous and induced psychosis was supplied by Abbott Laboratories, Harris Laboratories, Merck & Co., and the S. M. A. Corporation. The S. M. A. Corporation furnished the nicotinic acid used in the subclinical and mild cases. The nicotinic acid used for nutritional studies in children was supplied by Mead Johnson & Co. Coramine, the diethyl amide of nicotinic acid, was supplied by Ciba Pharmaceutical Products. The vitamin B₁ used in the study was furnished through the courtesy of Merck & Co.

† The majority of pellagrins in relapse excrete in the urine increased amounts of an ether-soluble substance, or substances, which gives the color of porphyrin in 25% HCl.¹⁷ The prompt disappearance of this substance from the urine following the administration of large amounts of nicotinic acid can be used as an early objective test. From our observations of some 600 patients, we have noted that the incidence of strongly positive tests was much greater during February and March than during May and June. We have observed, however, that the severity of the other manifestations of pellagra does not parallel the excretion of these ether-soluble substances in the urine. Dr. C. J. Watson, in a personal communication, has suggested that the color of this test may be due, at least in part, to mesobiliviolin, and has supplied us with pure mesobiliviolin which certainly gives a similar color. Further studies on this point are being made. It is interesting that the urine from dogs with spontaneous blacktongue does not give positive tests.

When one of this group entered the hospital, he was placed under the observation of one of the authors.* The method of study may be described as follows: A note was made of the mental symptoms and their apparent duration before entry and of their progress over a period of several days while the patient was in the hospital, maintained on a restricted diet and given no therapy. If no improvement in the mental symptoms occurred under these conditions, they served as an index for testing the potency of the therapeutic agent. A specific therapeutic agent is of value if the mental symptoms clear promptly in all cases when sufficient amounts of the substance are added as a supplement to the control diet, all other conditions remaining constant.

The 60 psychotic pellagrins were divided into four groups. Each pellagrin was observed during a control period which varied from 1 to 10 days. The first group was composed of 21 pellagrins who received from 100 to 200 gm. of glucose per day and drank water *ad lib.* during the control period; the second group was composed of 20 pellagrins who drank water but ate no food during the test period; the third group consisted of 10 pellagrins who were given only a basic diet⁴ and water *ad lib.* for from 2 to 3 days; the fourth group consisted of the remaining 9 pellagrins who were offered an ordinary hospital diet and water *ad lib.* (these patients refused to eat more than small amounts of food and their symptoms became worse). At the end of the control period, nicotinic acid, 500 to 1000 mg. daily, was administered orally to 49 of the patients. A total of 100 mg. daily, in 5 doses of 20 mg. each, was given intravenously or intramuscularly in 3 cases. Coramine ($C_{10}H_{14}OH_2$), the diethylamide of nicotinic acid, was administered orally in doses of 2 to 5 cc. daily to 8 of the 60 patients, until a total of from 20 to 50 cc. had been given. After improvement occurred every patient was placed on a well-balanced, high vitamin diet.

Observations. *The Curative Effect of Nicotinic Acid and Coramine on the Acute Mental Symptoms of Pellagra.* The severe psychoses of pellagra in the 60 patients who developed the psychosis spontaneously were relieved following the administration of coramine or nicotinic acid. Within 10 hours to 6 days after medication was begun, all of the patients had improved. So long as the patients were kept on a maintenance dose of nicotinic acid, no recurrence of symptoms was noted during the subsequent 2 to 4 months' period of observation. Similar studies with coramine are now being made.

The progress of a psychotic pellagrin under treatment with

* We were given invaluable assistance by the professional and administrative staffs of both hospitals, and are particularly indebted to Dr. J. B. McLester and Dr. Robert E. Stone; Miss Jean Grant, dietitian; Miss Ann Van Blaricom, Mrs. Verna Moore, and Miss Willadine Robbins, nurses; Miss Elisabeth Zschiesche, Miss Nelwyn Huff, and Miss Helen Grant, technicians; and Dr. Yasuo Sasaki, E. S. Gross, and S. P. Vilter, chemists.

nicotinic acid or coramine is probably best illustrated by the representative case report which follows:

CASE 1.—M. T. (No. 121169), a 55-year-old married negress, was brought to the Hillman Hospital on April 7, 1938, with hallucinations, delusions, dermatitis, diarrhea and stomatitis.

Medical history, family history and past history were not contributory.

Present Illness. The onset of the present illness was indefinite. For years the patient's diet had consisted chiefly of cornbread, black-eyed peas, fat meat, potatoes and greens. During the 2 to 3 weeks before admission, she had become progressively worse, developing anorexia; abdominal burning and discomfort ("like something eating my insides out"); nausea; diarrhea (20 to 25 stools per day), associated with tenesmus; burning and soreness of the mouth, tongue, and throat; increased salivation; burning and breaking out of the skin of the face, upper extremities and perineum; pain and tenderness of the genitalia associated with vaginal discharge; insomnia; nervousness; "foolishness and craziness in the head;" vertigo; loss of weight; and general weakness. During the week prior to admission to the hospital she had eaten little or no food because her mouth was too sore. The use of alcoholic beverages was denied.

Physical Examination. Physical examination, upon admission, revealed a well-developed, undernourished negress picking at the bedclothes, tossing about in bed, and requiring restraints.

Skin: Characteristic pellagrous dermatitis covered the greater portion of the ears, nose, face, malar prominences, forehead and lids of the eyes. In places these lesions were surrounded by a zone of erythema and slight tenderness. Pellagrous lesions also extended over the dorsa of the hands and upward around the wrists and over the ventromedial aspect of the arms. The affected skin appeared devitalized, darkly pigmented and was covered with many large blebs. The skin was broken over several of the joints. A similar pellagrous lesion, from 6 to 8 inches in diameter, was present in the suprasternal notch. The upper borders of this lesion extended to encircle the neck, thus forming a typical "collar of Casal." The skin of the legs was dry and rough. Areas around the hair follicles were deeply pigmented. The perineum presented a wide area of excoriation which was moist and covered with foul-smelling débris.

Mucous Membranes: Nose: The mucosa was fiery red, slightly swollen and partially covered with crusts.

Mouth: The lips were swollen and covered with crusts. The mucosa of the mouth and of the tongue, fauces and oral pharynx was reddened, slightly swollen, tender and presented many ulcers of varying size, the surfaces of which were covered with gray exudates. The tongue which was thick, reddened and tender had large ulcers on the ventrolateral surfaces. There was a striking increase in the flow of saliva (200 cc. per hour).

Vulva and Vagina: The former was swollen and tender. The mucosa of the vagina was fiery red, swollen, tender and contained several small ulcers.

Neuropsychiatric Examination. Upon admission the patient was apprehensive, disoriented and refused to talk in detail about the "foolishness and craziness in the head." She responded to questions and commands slowly or not at all. She had visual and auditory hallucinations which centered particularly around religious subjects and persons who wished to kill her, or animals and creatures which annoyed her. No impairment of memory was detected at the time of admission to the hospital, but she would not cooperate for mental testing. The motor and sensory systems were normal, with the exception of slight hypesthesia and hypalgesia of the distal portions of the upper extremities. This became progressively less in an ascending

manner, and the border where sensation became normal was not well defined. The tendon reflexes were very active; the plantar responses were flexor in type.

Laboratory Findings. Red blood cells, 3,800,000; hemoglobin, 67%; leukocytes, 7700 (neutrophils, 62%; lymphocytes, 38%). Blood Wassermann positive; spinal fluid Wassermann negative. The urine contained a trace of albumin, but otherwise was not abnormal, except for increased quantities of ether-soluble coproporphyrin (or some substance resembling it in ether solubility and color appearance in 25% HCl) before treatment.

Medication and Diet. During the first 96 hours of hospitalization, the patient was given daily 20 cc. of coramine orally, in 5 doses of 4 cc. each. During the first 36 hours she received, in addition to the coramine, only 10% glucose and water by mouth. Thereafter, as she became free from nervous and digestive symptoms she was given the regular hospital diet with the intermediate feedings of milk-egg mixture, as she desired, until discharge.

Progress. Within 12 to 16 hours after treatment was instituted, the ptialism had decreased and the mucosa of the mouth, tongue, nose and vagina appeared less swollen, red and tender. At the end of 24 hours, the fiery redness was replaced by a bluish-gray cast, and the salivary excretion was normal in amount. She asked for food and stated that this was the first time since the onset of her illness that she had been hungry.

After 48 hours, she became quiet and coöperative and had insight into her mental condition which we learned had been very distressing to her during the week prior to admission. This fact had not been fully appreciated at the time of the initial examination, partly because of her apprehensiveness, maniacal outbursts, and her hesitancy to discuss her symptoms. She stated that her head began to clear 24 to 36 hours after treatment, and that now she knew that the "craziness and foolishness in the head" was unreal. The following account of the symptoms present before admission was obtained at this time: She thought she was being poisoned and otherwise abused by her neighbors. She saw and heard monkeys, rats and cows running around her, and felt bugs, snakes and worms crawling on her. She had dizziness, blurring of vision and was "unable to remember things." She could not direct her attention toward her usual household duties, "because I couldn't keep my mind on it."

Improvement continued steadily: 36 hours after treatment had been instituted and while she was still on the glucose restricted diet, the mucosa of the mouth appeared normal, except at sites of deep ulceration; the vaginal mucosa had healed; the redness and swelling had subsided; and the skin showed signs of healing. At this time she took an adequate diet eagerly and within a week all pellagrous lesions had healed.

Temperature and heart rate: During the first 60 hours the temperature varied between 98.6° and 100° F., and the heart rate between 80 and 90.

She was discharged mentally clear and in good physical condition 9 days after admission.

Comment. It was learned from the histories obtained from the family and friends of the 60 patients of this group that psychotic behavior had been present from 1 to 83 days. Most of these patients had had some sign of psychosis from 1 to 2 weeks. After treatment was begun, recovery occurred in from 10 hours to 6 days.

It is to be understood that no pellagrin with a chronic psychosis of years' duration, of the type often found in custodial mental hospitals, was treated. We believe that the patients treated in this series, because of their severe mental symptoms, would have been

committed and thus might have become chronic types. The mental symptoms of these 60 pellagrins were of the severe acute type. Many of the patients were violent and severely hallucinated; others were severely depressed. It is difficult to describe the change in these patients after therapy was begun. The maniacal patients became calm; the depressed, cheerful; and, legally speaking, the insane again became sane. After recovery these patients often had an excellent memory of their actions, ideas, and of their surroundings during the psychotic period. They were usually completely adjusted after treatment, except for some perplexity about the cause of their actions during the psychosis. "What made me act that way?" and "Was I crazy?" are questions that are frequently asked at this time. In most cases improvement was abrupt, occurring sometimes overnight.

We have not observed a case of acute pellagra that has not responded promptly to nicotinic acid therapy, whereas our previous experience, as well as that of others, would indicate that these cases were likely to die if treated by ordinary methods and were almost certain to die if they went untreated.

Thirty cases, after relief from the acute psychoses of pellagra, have been kept free from mental signs by the continued use of nicotinic acid and without change in their previous environment. Recurrences of mental symptoms of similar severity in other patients have also been prevented¹¹ by the daily ingestion of large amounts of dried brewers' yeast (Harris Laboratories, Anheuser-Busch, Mead Johnson & Co).

Twenty other psychotic pellagrins with mental symptoms failed to maintain recovery induced by nicotinic acid when it was discontinued and the patient returned to his old environment. In our studies 2 years ago,¹⁵ we were able, by extraordinary effort on the part of the physicians and a large nursing staff, to feed the patients large quantities of a well-balanced diet and large amounts of dried brewers' yeast, in some instances supplemented by injections of liver extract. This treatment, when directed individually, was effective; but the convalescence was slow and the attention required for each patient is prohibitive on an ordinary ward of a general hospital. In contrast to the method applied in the above studies, the great majority of pellagrins do not have such individual attention. As a result, the mortality rate is high, and a considerable number of the patients who do improve make only a partial recovery and are subsequently sent to a hospital for the insane. This suggests that some systematic check should be made for cases of this nature in the large mental hospitals. Such studies are now under way.

The remaining 10 patients did not report for subsequent observation.

B. Pellagrins With Extensive Mucous Membrane and Dermal Lesions and Severe Gastro-intestinal Involvement, but No Mental Symptoms. An alternate method of study which we used was a comparative observation of the course of the disease in 15 pellagrins who had no mental symptoms but did have extensive skin and mucous membrane lesions and involvement of the gastro-intestinal tract. These patients, who were too ill to ingest an ordinary diet, were given 10% glucose solution. Certain of them developed psychoses while restricted to such a diet. If a medicament has therapeutic value under these circumstances, the acute mental signs which develop under controlled conditions should remit promptly if sufficient amounts of the substance are added to a glucose diet, all other factors remaining constant.

Observations. Within the 10-day period of observation, 10 patients in this group developed a psychosis and 5 did not. To 5 of the 10 cases who developed a psychosis, 500 mg. of nicotinic acid were administered daily in 10 50-mg. doses. This was the only supplement to the glucose diet. Prompt relief of the symptoms occurred in all cases. Before they were discharged from the hospital, all of the patients were given a high caloric, high vitamin diet in addition to nicotinic acid. No recurrence of symptoms was noted during the subsequent 2 to 4 months' period of observation.

A representative case report of a patient whose psychosis occurred on a glucose-restricted diet and who was cured promptly by the addition of nicotinic acid to the glucose, is given below.

CASE 2.—E. T. (No. 121883), a 31-year-old negro widow, was admitted to the medical service of the Hillman Hospital on May 10, 1938, complaining of weakness and diarrhea of about 5½ months' duration.

Family history and past history were irrelevant.

Present Illness. The onset of the present illness was insidious and occurred about 5½ months before admission, with the development of progressive general weakness; intermittent diarrhea; vaguely described general abdominal discomfort; loss of weight; and a bloody vaginal discharge. Six weeks before admission she was examined in the gynecologic and proctologic clinics, where the following diagnoses were made: Uterine fibroids, rectal stricture, mucous colitis and secondary anemia. Palliative therapy afforded only temporary relief and all of the above symptoms persisted and gradually became worse. During the 7 to 10 days before admission, signs of dermatitis (increased pigmentation, roughness, induration and slight tenderness) were present over the hands, forearms and elbows. She developed anorexia; soreness and burning of the mouth; increased salivary flow; burning discomfort in the epigastric and substernal region; nausea; increased weakness; nervousness; and, at times, vertigo. There was no emesis, personality change or symptoms of peripheral neuritis.

Physical Examination. The physical examination revealed a poorly nourished negress who appeared to be chronically ill. Temperature, 98° F., pulse 75, respiration 21, blood pressure 120/80.

The skin was dry, loose, rough and deeply pigmented, particularly over the bony prominences. Large, well-demarcated areas of pellagrous dermatitis were present over the dorsa of the hands, wrists, forearms, elbows and over the external genitalia, extending around the anus and down the

medial aspect of the thighs. There was a slight diffuse lesion of the buccal and lingual mucosa, characterized by swelling, redness, tenderness and increased salivary flow, but no ulceration. The vaginal mucosa was diffusely and moderately red and tender, and there was vaginal discharge. The vulva was swollen and tender, and presented several minute ulcers at the mucocutaneous junction. A grayish-white exudate surrounded the anus. Digital examination was not done because of extreme tenderness. The examination otherwise was not remarkable except for an enlarged, firm uterus.

Neuropsychiatric Examination. Reflexes were normal. The motor and sensory systems were normal. At times, the patient complained of nervousness and vertigo. No other positive psychiatric findings were detected.

Laboratory Findings. Red blood cells, 2,500,000; hemoglobin, 45%; white blood cells, 6600 (neutrophils, 87%; lymphocytes, 13%). Blood Wassermann negative. The urine was not remarkable except that it was positive for an ether-soluble substance, or substances, giving the color of porphyrin in 25% HCl.

Course. During the first 6 days in the hospital she was offered the regular hospital diet, but because of oral pain, refused to eat. She received paregoric and bismuth for the diarrhea. Her general condition slowly became worse. She was given only water and 2000 cc. of a 10% solution of glucose by mouth daily for the next 7 days. No other food or medication was given. During this period she became worse. She complained more than previously of the soreness of her mouth, tongue and vulva; dizziness; nervousness; insomnia; and burning of the feet. Examination of the mucosa at that time showed it to be ulcerated, more tender, and of a deeper red color. She developed severe vomiting and diarrhea, the ptialism increased and she became restless and appeared to be uncomfortable. Her illness continued to progress rapidly. Seven days after she had been subsisting on this diet of only glucose and water, the following progress note was made: "The mucosa of the mouth and tongue is fiery red and tender, and several large ulcers are now present over the buccal mucosa, fauces and pharynx; salivation has increased to 1500 cc. per day; the skin of the extremities is about the same as before, but that of the perineum is moist and partially excoriated. Her mental condition is now abnormal. She is disoriented as to time, reacts sluggishly, and is unable to recall recent events. She has visual and auditory hallucinations. She has developed insomnia and obviously is restless and confused." Her condition had become critical.

Nicotinic acid was begun at this time. During the next 48 hours she was given glucose and a total of 2000 mg. of nicotinic acid, in divided doses of 50 mg. each, by mouth. Before the 48-hour period of therapy was over, she had become quiet, seemed clearer mentally and slept without difficulty. She complained less of the soreness and tenderness of her mouth and tongue; the intense redness of the tongue had decreased remarkably, and the ptialism had decreased to 200 cc. per day. At this time the administration of nicotinic acid was discontinued and glucose was given as before. During the 48 to 72 hours after the treatment with nicotinic acid was discontinued, there was slight improvement of the condition of the mucosa. Her mental condition, however, became worse, and she was maniacal, anxious and confused, and again had visual and auditory hallucinations.

Nicotinic acid therapy was resumed, and a total amount of 1700 mg. of this substance was administered during the first 48 hours when improvement again took place. Thereafter, a total daily dose of 1000 mg. was given for a period of 1 week, during which time the patient also received a high caloric, high vitamin diet. The mucous membranes healed rapidly, the mental symptoms cleared completely, and within a week there was

considerable desquamation of devitalized skin. Her appetite, strength and general condition likewise were improved remarkably.

During both relapses there was an elevation in temperature from 98° to 100° F., and an increase in pulse from an average of 80 up to 95. The temperature and pulse rate returned to normal during the final week of hospitalization.

C. Subclinical and Mild Pellagrins. In the pellagra clinic at the Hillman Hospital, the pellagra-preventive effect of nicotinic acid has been studied in 199 patients who have had recurrences of pellagra each spring over a period of several years. The majority of these pellagrins have had one or more recurrences of some of the mental symptoms of pellagra each pellagra season since the onset of their disease. The patients reported weekly for examination, and at the time of each visit a record was made of their weight, physical condition and of any untoward sensations or changes in sensations of which they complained. They were also questioned carefully regarding any change in dietary habits and environment. All have been kept free from recurrences of their mental symptoms from February 15 to July 1, 1938, by the use of nicotinic acid administered in daily doses of 100 to 600 mg. No change worth noting has occurred in their environment or dietary habits.

It is noteworthy that many physicians who wrote on pellagra before the publication of Goldberger's work contended that pellagra should be classified in the group of neuroses. Every pellagrin has one or more symptoms which might be considered those of a neurosis. It is because of the multiplicity of these vague, subjective manifestations of which the pellagrin complains that one must be extremely wary in interpreting the state of bodily function and especially in evaluating neuropsychiatric disorders. The selection of patients has been most arbitrary and has in great part depended upon a knowledge gathered from previous studies of these patients. Particular stress was laid on choosing patients who, after previous periods of treatment, had no vague, indefinite complaints, thus eliminating those persons who had chronic complaints. We have attempted to observe specifically the relief of such prodromal symptoms of pellagra as fatigue, insomnia, anorexia, vertigo, paresthesias, palpitation, nervousness, headache, forgetfulness, apprehension and distractibility. This is manifestly a task fraught with danger. To mention one pitfall, the mere attendance at a "pellagra clinic" whose work has been favorably bruited about by word of mouth and otherwise, conceivably might be responsible for the relief of many symptoms. It was in an attempt to avoid suggestion that the following method was used in studying the effect of nicotinic acid on the "neuroses" of mild pellagra.

There were 225 patients in the pellagra clinic who did not come under observation early enough during the spring of 1938 to receive nicotinic acid as a preventive measure. At the time of examination

these patients had developed mild pellagra and some of the above symptoms. They were arbitrarily given one of four medicaments, all of which were similar in appearance: 75 received acetylsalicylic acid; 50 received sodium bicarbonate; and 100 were given vitamin B₁.

Observations. Following the administration of nicotinic acid to subclinical pellagrins with prodromal symptoms and to mild pellagrins with the same type of symptoms, there is prompt relief.* During the spring and summer seasons of 1938 the great majority of these patients has remained free from a return of these prodromal symptoms, as long as adequate amounts of nicotinic acid were administered frequently. In a number of instances, however, the symptoms were returning and we found it necessary to increase the daily dosage of nicotinic acid. In some cases, we have had to give as much as 600 mg. per day, in order to keep these persons free from such symptoms. The patients receiving the other three medicaments reported little or no change in symptoms. Some described relief during the first few days, after which time they stated that the medicine did not help. Without their knowledge the medication of all of the patients in this group was later changed to nicotinic acid. In each case, following the administration of nicotinic acid, there was prompt relief of the majority of the neurotic symptoms. On nicotinic acid therapy the ambulatory pellagrin regained energy and appetite and many resumed work. This striking relief occurred within 1 to 12 days following the administration of 5 or 6 doses of 100 mg. each per day (often a smaller dose was effective). This improvement has been almost universal in this group of cases. We do not claim, however, that the administration of nicotinic acid will be followed by complete relief of the same symptoms if unassociated with pellagra.

Probably of greater significance than the relief of "neurotic" symptoms following the administration of nicotinic acid is the return of these symptoms when, without the patient's knowledge, nicotinic acid is withdrawn and another medicament of similar appearance is substituted for it. When nicotinic acid was withdrawn suddenly during a period when the patient was obtaining benefit from it, the original subjective manifestations usually returned within a week.

Spies and Aring¹² have reported that vitamin B₁ is beneficial in treating the manifestations of peripheral neuritis associated with pellagra, but that it does not cure the alimentary and central nervous system disturbances of pellagra. Studies on a large number

* Preliminary studies on 75 children with characteristic pellagra have shown that the majority of them have dizziness, irritability, stomach upsets, flight of ideas, and inability to get along well in school or with other members of their family. These symptoms usually disappeared promptly following the ingestion of tablets of nicotinic acid.

of mild pellagrins who were given vitamin B₁ have shown that the mental symptoms grow progressively more severe on vitamin B₁ therapy, but respond promptly following the administration of nicotinic acid. This investigation is being continued, but the following 2 cases illustrate this point:

CASE 3.—L. M. F. (Clinic case), a 27-year-old white female, was first seen in the clinic of the Hillman Hospital on May 14, 1938, chiefly because of pain and burning of the feet and legs of about 2½ months' duration.

Family History. Two members of her family have had pellagra.

Past History. This patient had "pellagra," or an illness similar to the present illness, in the spring of 1934 and since that time has had 2 recurrences of the disease each year, in the spring and late summer.

Present Illness. The onset of the present illness was insidious. About 2½ months before admission the patient developed itching and burning of the skin of the upper extremities and, to a less extent, of the face, neck and shoulder girdle. Later these areas became intensely red and deeply pigmented. As the disease progressed the patient developed soreness and burning of the tongue and mouth; anorexia; ptyalism; constipation; general weakness; loss of weight; nervousness; increased irritability; vertigo; impairment of memory; insomnia; "foolish dreams;" and burning and pain in the feet and legs. These symptoms slowly became worse. During the week prior to the patient's first visit to the clinic, the pain in her feet and legs became considerably worse and was associated with swelling and numbness.

Her usual weight was about 117 pounds; at the time of admission it was 104 pounds. There was no evidence of pellagra when the patient was first seen in the clinic, but she had peripheral polyneuritis, most marked in the lower extremities.

Her diet had consisted chiefly of carbohydrates but also included small amounts of green vegetables. She ate very little lean meat, eggs or milk.

Course. No therapy was prescribed when the patient first visited the clinic on May 14. Four days later consultants concurred in the diagnosis of peripheral neuritis, and she began taking vitamin B₁ in amounts of 10 mg. daily (tablet form). Ten days later she returned to the clinic and reported considerable relief from anorexia and from the burning in her feet, but she complained of generalized aching. At that time the dosage of vitamin B₁ was increased to 40 mg. daily. She was confused, and said that she worried too much and could not concentrate. Three days later she had no discomfort in her feet but she complained at that time of diarrhea (up to 9 stools per day), abdominal cramps, nausea, emesis several times, slight soreness of the mouth and tongue, and increasing weakness of 3 days' duration. Nicotinic acid, 300 mg. daily, was prescribed along with the vitamin B₁. Within a few days the soreness of her mouth and tongue and the "slobbering" (ptyalism) disappeared, and within a week the diarrhea and abdominal discomfort had subsided. Her appetite, strength, nervousness and vertigo also improved progressively. She said that she had not felt better in months. Before treatment with nicotinic acid the urine repeatedly contained ether-soluble substances giving the color of porphyrin in 25% HCl. The urine, 48 hours after treatment with nicotinic acid, was negative for such substances.

CASE 4.—E. B. (Clinic case), a 35-year-old white married woman, came to the clinic for the first time on May 18, 1938, because of pain and burning of the feet and legs, accompanied by characteristic pellagrous dermatitis and glossitis.

Family history was irrelevant.

Past History. She had pellagra for the first time during the spring of 1936 and had a recurrence the following spring. The symptoms of these illnesses were similar to those of the present illness.

Present Illness. The onset was insidious. About 2½ months before her first visit she developed dermatitis of the hands, arms, feet and legs; soreness and burning of the mouth and tongue; ptyalism; general abdominal discomfort; nausea; vertigo; emesis on occasion; anorexia; diarrhea; headache; nervousness; insomnia; impairment of memory; sharp, shooting and aching pains; burning and slight swelling of the feet and legs; loss of weight; general weakness; cardiac palpitation and exertion; vaginal discharge; and itching and burning of external genitalia. These symptoms varied considerably in severity from time to time, and her general condition steadily became worse. There was excruciating tenderness to pressure in the extremities. The patient had mild pellagra and peripheral neuritis as evidenced by tenderness of the nerve trunks and loss of tendon reflexes in the legs.

Course. During the first 4 days she was given 10 mg. of vitamin B₁ daily by mouth and, thereafter, 20 mg. per day. During the first 10 days of vitamin B₁ therapy her appetite improved and the burning, pain and swelling of her feet and legs subsided completely. However, during the following week she became remarkably worse, her husband reporting that she had been "crazy" and did not know what she was doing. She was extremely dizzy; unsteady on her feet (had to be assisted in walking); talked incoherently; had visual and auditory hallucinations; was disoriented as to time, place and person; and complained of being "numb all over." At this time, 10 days after first coming to the clinic, she was given, in addition to the vitamin B₁, 500 mg. of nicotinic acid daily.

During the following 12-day period there was progressive improvement in her general condition. She said she felt "a lot better," did not appear confused, "knew what she was doing," her appetite was better and the aching had disappeared. Her husband stated that she was now mentally well. Her diet and environment remained the same throughout the study, except that the patient refused to eat much of what was offered to her until vitamin B₁ therapy was instituted.

Laboratory Findings. Red blood cells, 3,250,000; hemoglobin, 63%. As in the preceding cases, the urine on repeated examination contained an ether-soluble substance giving the color of porphyrin in 25% HCl, which disappeared following treatment with nicotinic acid.

Comment. The manifestations of peripheral neuritis of pellagra improved promptly following the administration of large amounts of vitamin B₁. The present study, which is being continued and which will be reported in detail later, shows that vitamin B₁ does not cure the mucous membrane lesions or the mental symptoms of pellagra, but that it does aid in curing the peripheral neuritis.

D. Patients With Psychoses Not Associated With Pellagra. The effect of nicotinic acid on the mental symptoms of pellagra led to the thought that this substance might be efficacious in the treatment of other psychoses. This might be expected to be the case, especially in psychoses alleged by some to be related to deficiency states other than pellagra; for example, alcoholic hallucinosis, delirium tremens, and Korsakow's psychosis. Accordingly, we administered nicotinic acid to twenty-six patients suffering from the following mental diseases: alcoholic hallucinosis, Korsakow's psy-

chosis (following chronic alcoholism), manic depressive psychosis (depressed phase), involutional psychosis, psychosis with cerebral arteriosclerosis, and schizophrenia. The amount of nicotinic acid was rather large (1 to 2 gm. daily in divided doses); it was given as a supplement to a regular house diet and the period of treatment was as long as 50 days in some cases. This treatment was without psychiatric results in these cases. However, it caused flushing and a feeling of warmth in the skin, as described in detail recently by Spies, Bean and Stone.¹⁴ It is our impression, therefore, that the psychoses are benefited only if they are a part of the syndrome of pellagra.

Summary and Conclusions. 1. The present studies suggest that nicotinic acid in adequate amounts is a specific therapeutic agent for the acute mental symptoms of pellagra. Both spontaneous and induced psychoses of pellagra respond promptly following this therapy. Coramine, the diethyl amide of nicotinic acid, also is beneficial in the treatment of the abnormal mental symptoms.

2. The psychoses present in 26 non-pellagrous persons did not improve following the ingestion of these drugs.

3. The so-called "prodromal" or "neurotic" symptoms of pellagra usually disappear following the administration of nicotinic acid. These studies were conducted in such a manner that suggestion was eliminated, and they indicate that the vague, subjective, prodromal symptoms are evidence of disordered function.

4. These studies show that frequently repeated large doses of nicotinic acid prevent the development of mental symptoms in sub-clinical pellagrins and in mild pellagrins.

5. The minimal dose of nicotinic acid has not been determined but seems to vary from case to case. It is tentatively recommended that each patient with severe mental symptoms receive a total of at least 500 mg. per day. It is preferable to give this in 10 doses. In the extremely severe cases convalescence seems to be shortened by the administration of 1000 mg. daily. Since nicotinic acid is only one of the essential chemical substances present in the well-balanced diet, we suggest that all patients with pellagra be given a well-balanced diet whenever possible, even though nicotinic acid is used as a supplement.

6. The methods which have been described appear to offer a lead in the study, under controlled conditions, of one type of mental disease before, during and after mental signs are in evidence.

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STUDIES IN ALCOHOL.

I. THE DIAGNOSIS OF ACUTE ALCOHOLIC INTOXICATION BY A CORRELATION OF CLINICAL AND CHEMICAL FINDINGS.

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THE diagnosis of borderline cases of acute alcoholism has always been difficult. Because of the close association of alcohol with trauma, crimes of violence, automobile accidents and the like, the medico-legal aspect of alcoholic intoxication has become of great importance. Testimony based upon clinical findings alone is insufficient proof in a majority of cases to most courts and juries. The ability to demonstrate the presence of alcohol in a given individual would be definitely desirable. Of still greater importance and significance would be the ability to determine whether a given amount of alcohol is sufficient to produce intoxication.

It was believed that a study correlating the clinical findings of acute alcoholism with the concentration of alcohol in the blood and urine in a large series of cases might give definite chemical standards for the diagnosis of the condition. Consequently, a total of 1159 patients admitted to this hospital with a pre-admission diagnosis of acute alcoholism have been studied with regard to this correlation over a 3-year period.

Others have performed like studies, the major part of the work coming from foreign authors. Hoffman,⁵ reporting 642 cases, stated that intoxication occurred in 100% of all cases when the concentration of alcohol in the blood was 0.20 to 0.25% and above. Widmark¹¹ and Schwarz,⁹ in 592 and 905 cases respectively, found intoxication in all cases in concentrations of 0.25 to 0.30% alcohol in the blood or over.

Comparatively few data have been reported from this country. Bogen,¹ analyzing 250 cases in which alcohol was present in the urine, concluded that intoxication occurred in most cases in concentrations over 0.20% alcohol. The blood alcohol content of 200 intoxicated cases was reported by Johnson⁷ but no evaluation of his results are possible because of the scarcity of data in the article. Turner¹⁰ investigated 32 cases and believed that intoxication occurred in most cases when the concentration of alcohol in the blood varied from 0.20 to 0.30%. Harger,³ in 140 cases, found 100% intoxication in alcoholic concentration in the blood of 0.20 to 0.25% or over.

Methods. The method of the determination of the alcohol content of the blood and urine as devised by Heise⁴ in 1934 was used. It utilizes the reducing power of alcohol to decolorize potassium dichromate in acid solution.

On admission 5 cc. of blood were withdrawn from the median basilic vein and transferred to an oxalate bottle. Precautions were taken to have the arm wiped dry of alcohol used for sterilizing purposes before taking the sample. When possible a sample of urine was also obtained.

Blood. Two cc. of oxalated blood were placed in an 800-cc. Kjeldahl flask and about 15 cc. of a picric-tartrate reagent were added. (Picric-tartrate reagent—one-half saturated picric acid containing about 10% tartaric acid.) The resulting mixture was distilled and the first 10 cc. of the distillate collected. An aliquot portion, 2 cc. and fractions of this amount, were then added to separate tubes containing 1 cc. of potassium dichromate solution (N/15 $K_2Cr_2O_7$ in 50% H_2SO_4), the final volume being made up to 3 cc. in all tubes. They were then placed in a boiling water bath for 10 minutes and compared with standards containing known amounts of alcohol. Results were expressed in terms of percentage of alcohol by weight per 100 cc. of blood.

Specificity. While the method is not specific for ethyl alcohol, the blood distillate of non-alcoholics ordinarily contains no other reducing substances. Blood specimens taken from 44 patients on various wards of the hospital were negative for volatile reducing substances. Acetone bodies may interfere but may be detected and eliminated by qualitative tests. The highest reading in terms of alcohol percentage obtained from 7 patients with 4+ acetone was only 0.03% alcohol. Ether and paraldehyde have no reducing power. Blood taken from patients following full ether anesthesia and from 13 cases of paraldehyde poisoning exhibited no reducing properties with this method. Methyl alcohol will interfere but may also be detected by appropriate qualitative tests.

Urine. A mixture of 10 cc. of urine and 10 cc. of the picric-tartrate reagent was distilled and the first 10 cc. of the distillate was collected. One cc. and fractions of this amount were added to tubes containing 3 cc. of the dichromate solution, the final volume being made up to 4 cc. in all tubes. They were then placed in a boiling water bath for 4 minutes and compared to known standards. Results were expressed in terms of percentage of alcohol by weight per 100 cc. urine.

Specificity. The urine of individuals taking urotropine may exhibit volatile reducing properties providing formaldehyde has been produced in the kidneys. The highest reading in terms of alcohol concentration in a series of cases using urotropine in the usual dosage was 0.05% alcohol. Formaldehyde, therefore, should be eliminated as an interfering agent by

qualitative methods.* Acetone bodies are also volatile reducing substances but have never shown readings higher than 0.03% in terms of alcohol concentration. No other volatile reducing agents were detected in the urine of a group of over 200 non-alcoholics.

TABLE 1.—CLINICAL CRITERIA ESSENTIAL FOR DIAGNOSIS OF CLINICAL INTOXICATION.

- I. Patient *must* have a gross gait abnormality or be unable to walk.
- II. In addition to I, at least two of the following tests *must* be positive.
 1. Gross abnormality of speech or unable to speak.
 2. Flushed face.
 3. Dilated pupils.
 4. Alcoholic odor of breath.

Clinical Material. A. *Criteria for Diagnosis of Clinical Intoxication.* The following criteria were adopted for the clinical diagnosis of acute alcoholic intoxication. As shown in Table 1, gross gait abnormality must be present, and in addition at least two of the following tests must be positive: abnormality of speech, flushed face, dilated pupils and alcoholic odor of the breath. In the detection of gait abnormalities the individual was asked to walk from one side of the room to the other. If gross swaying, reeling or staggering were not present, the test was considered negative. For a detection of speech abnormality, the patient was required to answer simple questions only such as his name, residence, and so on. If definite slurring or incoherence was not present the test was considered to be negative. If the individual was comatose and was unable to walk or talk, final decision as to whether or not the defects were produced by alcohol was determined by subsequent ward observation.

B. *Analysis of the Cases.* A total of 1159 consecutive cases admitted with a pre-admission diagnosis of acute alcoholism were studied. In 1150 cases blood was obtained for analysis: 1000 cases were alcohol-positive and 150 alcohol-free. In 372 of the 1000 cases showing alcohol in the blood, the urine was also obtained for analysis. In 9 cases only the urine was obtained in all of which alcohol was present.

Of the 150 cases who were free of alcohol at admission, 78 were known chronic alcoholics. Table 2 shows the correct diagnosis in the other 72 cases. It is interesting to note the various conditions which may be confused with acute alcoholism particularly if the patient is comatose, which condition was present in 37 cases. Of these, 16 resulted from overdosage of either paraldehyde or barbital derivatives, while diabetes mellitus, uremia, cerebral injuries, cardiovascular accidents and schizophrenia accounted for nearly all others. The remaining 36 cases occurring in non-alcoholics were admitted in a non-comatose condition.

* One gram phloroglucinol is dissolved in 100 cc. of 10% NaOH; 0.1 cc. of this reagent added to 1 cc. of the distillate produced a red color in the presence of formaldehyde.

TABLE 2.—CORRECT DIAGNOSIS OF ALCOHOL-FREE CASES WITH PRE-ADMISSION DIAGNOSIS OF ACUTE ALCOHOLISM.

<i>Correct diagnosis.</i>	No. of cases.	No. of cases comatose.
Barbital poisoning	15	8
Paraldehyde poisoning	13	8
Cardiovascular accidents	11	5
Schizophrenia	7	2
Fractured skull	7	7
Psychosis	4	1
Epilepsy	3	1
Diabetes mellitus	2	2
Septicemia	2	0
Uremia	2	2
Anemia	2	0
Acute appendicitis	1	0
C.N.S. lues	1	1
Ruptured bladder	1	0
Ruptured gastric ulcer	1	0
Total	72	37

TABLE 3.—NUMBER AND PERCENTAGE OCCURRENCE OF DESIGNATED CLINICAL CRITERIA IN 1000 CASES WITH ALCOHOL IN THE BLOOD.

<i>Clinical criterion.</i>	No. of cases with positive clinical criterion.	Per cent positive clinical criterion.
Alcoholic odor	903	90.3
Abnormality gait or inability to walk	750	75.0
Abnormality speech or inability to talk	721	72.1
Dilated pupils	713	71.3
Flushed face	606	60.6

In Table 3 are tabulated the number of positive clinical tests with their percentage occurrence in the 1000 cases showing alcohol in the blood. It will be seen that an alcoholic odor was present in the greatest number of cases, namely 903 (90.3%). Gait and speech abnormalities were found in 750 and 721 cases respectively. In most instances, abnormality of speech accompanied an abnormality of gait. The incidence of dilated pupils closely followed, occurring in 713 cases, while that of flushed face was lowest with a total of 606 cases.

Using the criteria for acute clinical intoxication as outlined in Table 1, a diagnosis of the condition was made in 740 cases (74%). Of the 5 clinical criteria, examination of locomotion was most important since the diagnosis of clinical intoxication could not be made in its absence. There were only 10 instances in the entire group in which a gait abnormality was unassociated with less than 2 of the other clinical criteria, thus making a positive diagnosis impossible. In many of the 740 cases in which the clinical diagnosis has been made, not only 2 but even 3 or 4 of the other clinical criteria were found associated with the gait abnormality.

Alcohol was found in the urine of 381 cases, all but 9 of whom were included in the group of 1000 cases showing alcohol in the blood. In Table 4 are tabulated the number and percentage occur-

rence of the 5 designated clinical criteria in these 381 cases. An alcoholic odor to the breath was found in 88.8% (339 of the 381 cases). Gait and speech abnormalities were found in 287 and 267 cases, a percentage occurrence of 75.3 and 70.1 respectively. Dilated pupils occurred in 259 cases (68%) while a flushed face was found in the fewest number, 220 (57.7%). Using the same clinical criteria for the detection of drunkenness as previously outlined, a positive clinical diagnosis was made in 75.3% (283 cases). In only 4 instances was a gait abnormality encountered without a diagnosis of clinical intoxication being made.

TABLE 4.—NUMBER AND PERCENTAGE OCCURRENCE OF DESIGNATED CLINICAL CRITERIA IN 381 CASES WITH ALCOHOL IN THE URINE.

Clinical criterion.	Number positive clinical criterion.	Per cent positive clinical criterion.
Alcoholic odor	339	88.8
Abnormality gait or inability to walk . . .	287	75.3
Abnormality speech or inability to talk . .	267	70.1
Pupils, dilated	259	68.0
Flushed face	220	57.7

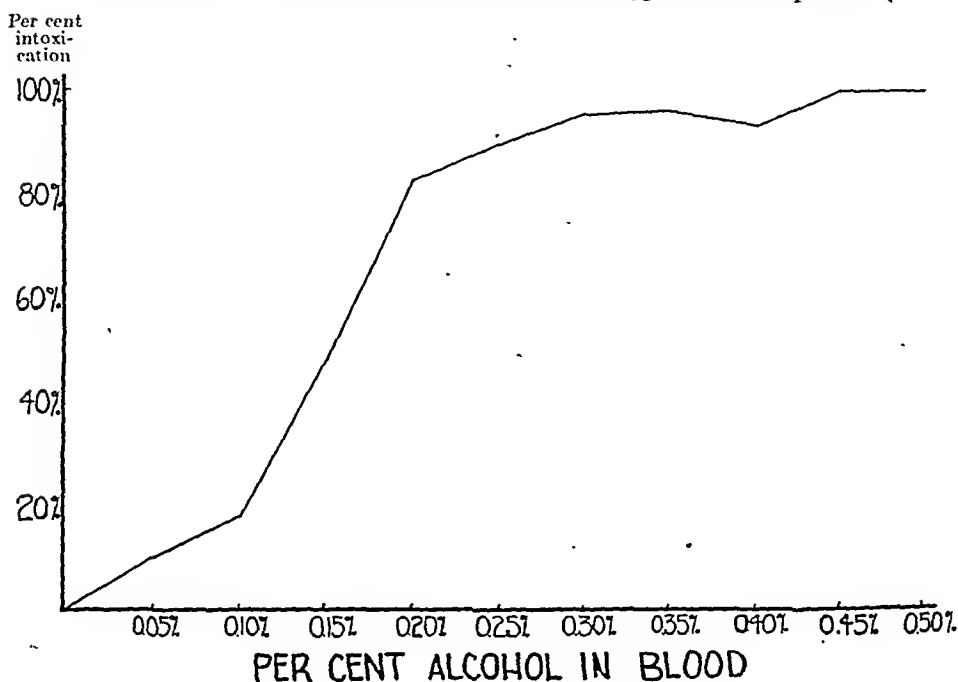
Chemical Results. 1. BLOOD. A. *Correlation of Occurrence of Acute Alcoholic Intoxication With Varying Alcoholic Concentrations.* The 1000 cases showing alcohol in the blood were divided into groups showing definite levels of alcoholic concentration, namely, 0.05% (including from 0.005 to 0.075%), 0.10% (from 0.075 to 0.125%), 0.15% (from 0.125 to 0.175%), 0.20%, and so on. The number and proportion of cases in each of the various groups are shown in Table 5. The largest number of cases, 330, occurred in the group 0.20% alcohol. A total of 779 cases occurred in the groups of 0.15 to 0.30% alcohol, inclusive. In the group 0.05% alcohol, were found 38 cases and 74 at 0.35%. Fifteen cases were found in the group 0.40% alcohol. Only 7 cases were found in the combined groups of 0.45 and 0.50% alcohol.

TABLE 5.—NUMBER AND PERCENTAGE OCCURRENCE OF ACUTE CLINICAL INTOXICATION AT VARYING GROUPS OF ALCOHOL CONCENTRATION. (Blood—1000 cases.)

Groups alcohol concentration:	0.05 %.	0.10 %.	0.15 %.	0.20 %.	0.25 %.	0.30 %.	0.35 %.	0.40 %.	0.45 %.	0.50 %.	Total.
Total number of cases . . .	38	87	132	330	176	141	74	15	5	2	1000
Number of cases intoxicated	4	16	61	276	158	133	71	14	5	2	740
Percentage cases intoxicated	10.5	18.4	47.0	83.6	90.0	95.1	96.0	93.3	100	100	74.0

Also in Table 5, and in Graph 1, the cases in which a clinical diagnosis of acute alcoholism was made are grouped at the various levels of alcoholic concentrations in the blood. Four cases (10%) of the 38 cases falling in the group at 0.05% alcohol were intoxi-

cated. In the group of 0.10% alcohol, 16 of 87 cases (18.4%) were inebriated. The incidence of drunkenness then rose rapidly; 47% in group 0.15% alcohol, 83.6% at 0.20%, and 90% at 0.25% alcohol. At 0.30% alcohol the incidence of inebriation was 95.1%. Intoxication was present in 96 and 93.3% of cases at groups 0.35 and 0.40% alcohol respectively. In the concentration brackets 0.45 and 0.50% alcohol, all cases were drunk. Severe intoxication usually was present at 0.35 and 0.40% alcohol. At group 0.40% alcohol, only 1 of 15 cases was considered not intoxicated according to our standards while coma was present in 8 cases. Two individuals died at concentrations of 0.47 and 0.48% alcohol respectively

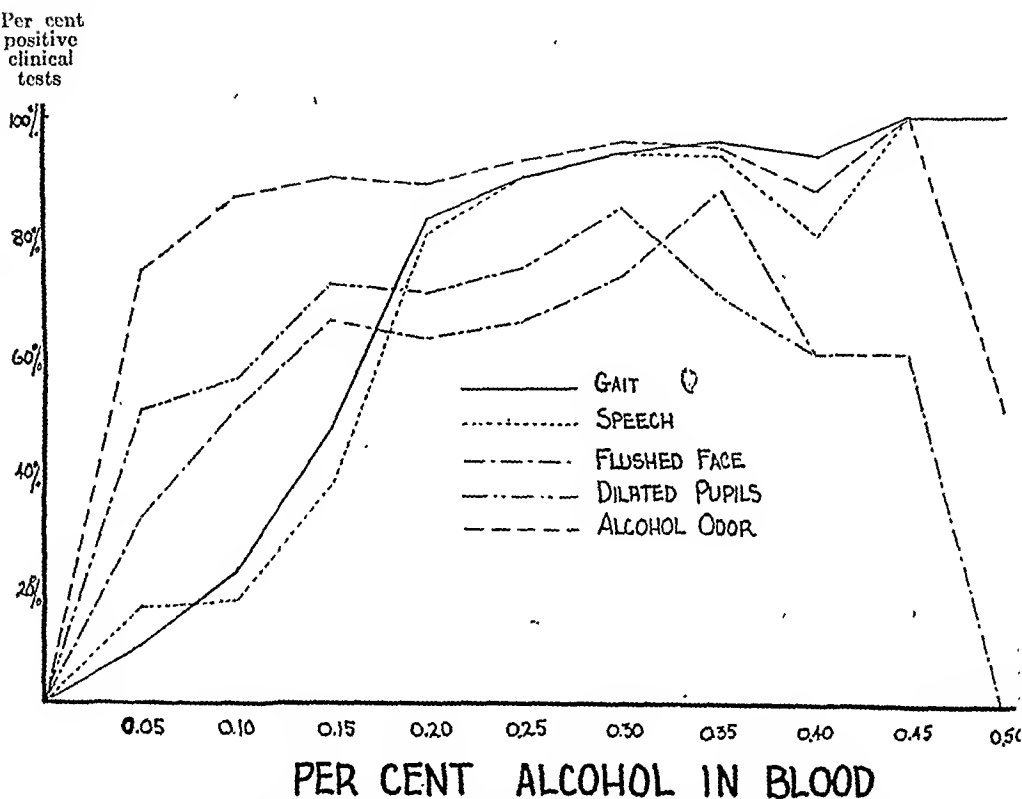


GRAPH 1.—Percentage occurrence of clinical intoxication at various concentrations alcohol; blood, 1000 cases.

from acute alcoholism as substantiated by postmortem findings. No cases with concentrations exceeding 0.50% alcohol were observed.

B. Correlation of Designated Clinical Criteria With Varying Alcoholic Concentrations. An analysis of the 1000 cases showing alcohol in the blood was made in respect to the occurrence of clinical criteria at the various alcoholic concentrations (Graph 2). The curves representing gait and speech abnormalities follow closely the curve of clinical intoxication as depicted in Graph 1. At the concentration groups 0.05 and 0.10% alcohol both gait and speech abnormalities were present in less than 20% of the cases. The percentage of occurrence at 0.15% alcohol was approximately 40% of the cases

and at 0.20% alcohol, approximately 80% of the cases. Both curves then gradually approached 100% which occurred in group 0.45% alcohol. In most instances, gait abnormality occurred slightly more frequently than did abnormality of speech. The incidence of alcoholic odor was high at all concentrations of alcohol, never dropping lower than 73% at group 0.05% alcohol. The incidence of dilated pupils and flushed face did not follow the curve representing the incidence of clinical intoxication. While the incidence of both of these criteria rose somewhat with increasing concentrations of alcohol (approximately 80% of cases at groups 0.30



GRAPH 2.—Percentage occurrence positive clinical tests at various concentrations alcohol; blood, 1000 cases.

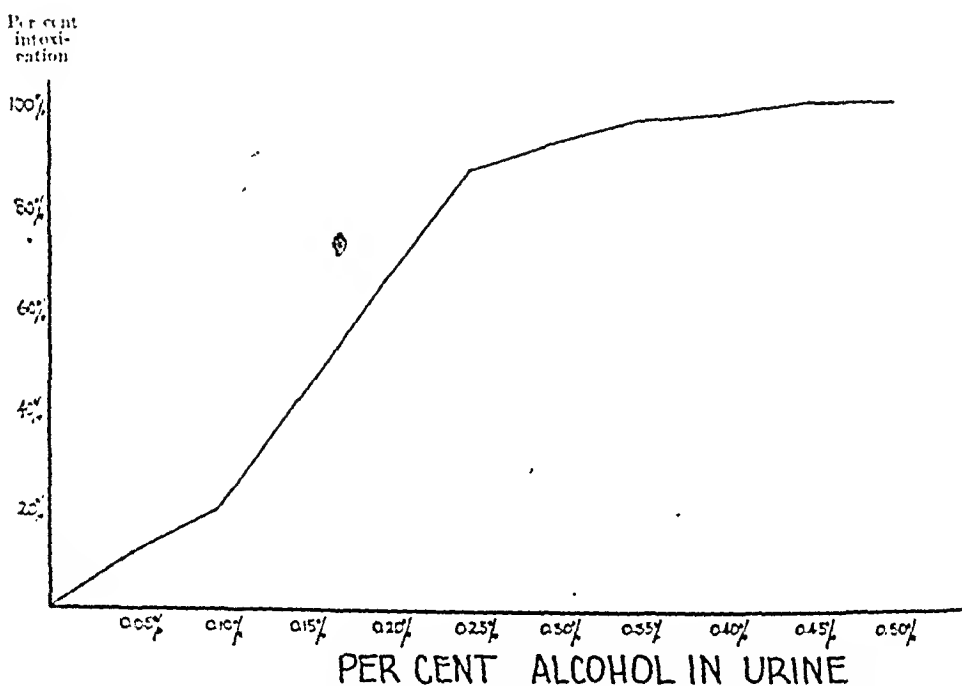
and 0.35% alcohol), their percentage occurrence decreased with still higher levels.

2. URINE. A. *Correlation of Occurrence of Acute Alcoholic Intoxication and Designated Clinical Criteria With Varying Alcoholic Concentrations.* Of the 381 cases showing a positive test for alcohol in the urine, 372 were included in the 1000 cases in which alcohol was found in the blood. No cases were observed with a positive urine and a negative blood or *vice versa*. The urinary concentration of alcohol was usually higher than that in the blood. The average ratio of the alcoholic concentration of the blood and urine in these 372 cases was blood to urine as 1 to 1.23 (range: from 1 to 2.3

to 1 to 1). In actual percentage of alcohol, the greatest variation was found in 1 case with 0.19% alcohol in the blood and 0.30% in the urine.

TABLE 6.—NUMBER AND PERCENTAGE OCCURRENCE OF ACUTE CLINICAL INTOXICATION AT VARYING GROUPS OF ALCOHOLIC CONCENTRATION.
(Urine—381 cases.)

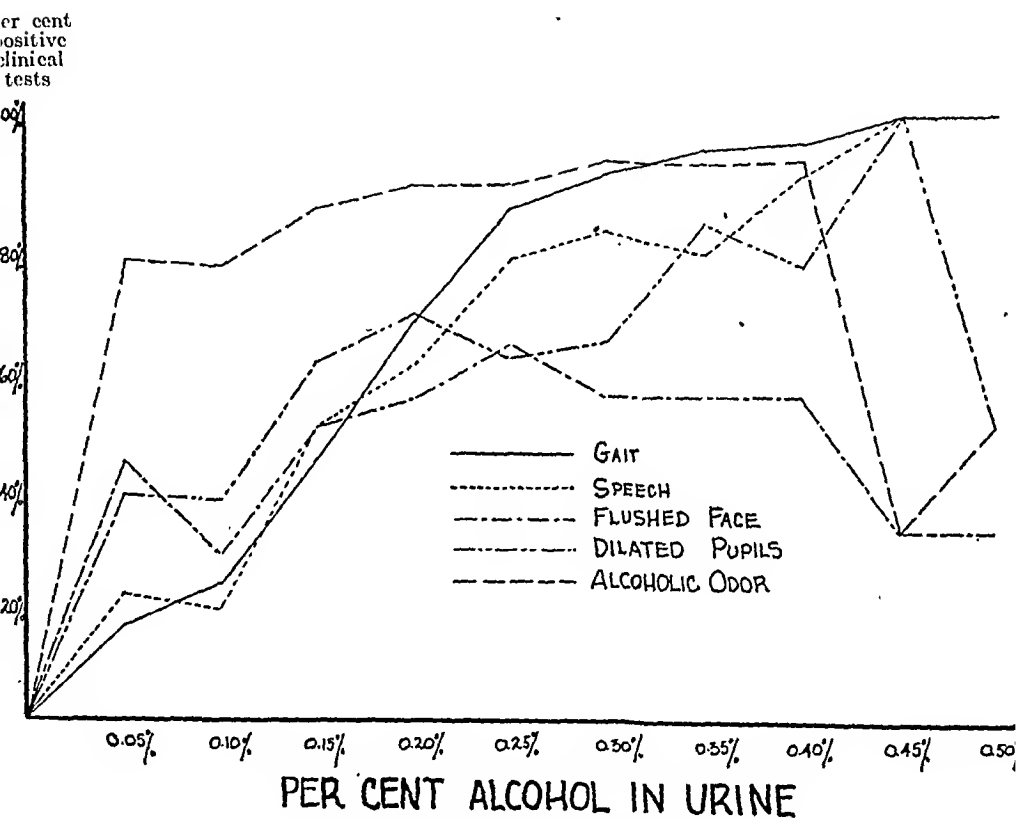
Groups alcohol concentration:	0.05 %	0.10 %	0.15 %	0.20 %	0.25 %	0.30 %	0.35 %	0.40 %	0.45 %	0.50 %	Total.
Total number of cases . . .	18	26	36	61	66	95	44	30	3	2	381
Cases intoxicated . . .	2	5	15	40	57	88	42	29	3	2	283
Percentage cases intoxicated	11.3	19.2	41.7	65.0	86.4	92.6	95.5	96.7	100	100	75.3



GRAPH 3.—Percentage occurrence of clinical intoxication at various concentrations alcohol; urine, 381 cases.

The 381 cases were placed in various groups of alcoholic concentrations in a manner similar to that used in the blood (Table 6). The greatest number of cases were found at group 0.30% alcohol, a total of 95 (25%) of the cases. In the groups of 0.20 to 0.35% alcohol inclusive, there were 266 cases (70%). Below group 0.20% alcohol a total of 80 cases was found. Thirty-five cases were encountered in groups 0.40, 0.45 and 0.50% alcohol. No cases were observed showing a concentration above 0.50% alcohol.

The cases in which a clinical diagnosis of acute alcoholism was made are shown grouped at the various brackets of alcoholic concentration in the urine in Table 6 and Graph 3. A definite rise in the occurrence of inebriation is noted after a comparatively low incidence of from 10 to 19% of the cases in the groups 0.05 and 0.10% alcohol respectively, to 41 and 65% of the cases at groups 0.15 and 0.20% alcohol. At 0.25% alcohol, the percentage of intoxication had risen to 86%. At 0.30% alcohol, 88 of 95 individuals (92.6%) were drunk. The incidence rose slightly at 0.35 and 0.40% alcohol to 95 and 97% respectively, while at levels above this concentration all cases were intoxicated.



GRAPH 4.—Percentage occurrence positive clinical tests at various concentrations alcohol; urine, 381 cases.

An analysis of the urine series in respect to the occurrence of clinical criteria at various groups of alcohol concentration is shown in Graph 4. The curves representing gait and speech abnormalities closely follow the incidence of clinical intoxication as shown in Graph 3. An alcoholic odor was present in a high percentage of cases at all levels. The curves of dilated pupils and flushed face rises slightly higher with increasing concentrations of alcohol but drops somewhat at the higher levels.

Discussion. In the beginning of this study, it was found necessary to adopt definite criteria for the clinical diagnosis of acute

alcoholism, a procedure which apparently has not been regularly used in other studies. In general, however, loss of muscular co-ordination has been considered a necessary finding for the diagnosis. In an analysis of a series of this size, namely 1159 cases, the clinical diagnosis of acute alcoholism could be made consistently only on the basis of some definite stipulated combinations of physical findings. In this manner, individualization of the single case was avoided and a logical treatment of all cases in exactly the same manner was accomplished. Thus, a positive diagnosis has been made only upon gross physical departure from normal. We have required gait abnormality as an absolutely essential finding in association with any 2 of 4 other findings, namely, abnormality of speech, alcoholic odor of breath, flushed face and dilated pupils. In the determination of incoördination of locomotion, gross swaying, staggering or reeling must be present, ascertained by having the individual walk from one side of the room to the other. More delicate tests of incoördination, such as the finger-to-nose test, or to walk a straight line, have not been used, because such tests are difficult to evaluate and are of too sensitive a nature. The elimination of the personal equation in the determination of the type of speech was accomplished by having the patient answer to familiar questions only, such as his name, age, residence, and so on. In contradistinction, the other 3 findings were not subject to the human element at least to a great degree. The diagnosis of acute alcoholism as made upon these criteria becomes, it is believed, a definite entity, which would be corroborated by most examiners.

Of the 5 clinical criteria, an alcoholic odor occurred most frequently, 90% of the cases, whether clinical intoxication was diagnosed or not. The other 4 criteria were found in 60 to 75% of the cases. There was considerable variation of their incidence at the different groups of alcoholic concentration found in both blood and urine. No correlation was noted when comparing the incidence of alcoholic odor, flushed face and dilated pupils with the incidence of clinical intoxication. The number of cases showing flushed face and dilated pupils was relatively small at low concentrations of alcohol, but rose to higher levels at concentration groups of 0.20 to 0.35% alcohol inclusive. At concentrations exceeding 0.35% alcohol, dilated pupils and flushed face were not seen so frequently. Most of the cases at these high concentrations were in coma and had the well-known pale skin and constricted pupils of alcoholic coma. It would appear that these 3 findings, alcoholic odor, flushed face, and dilated pupils could be considered significant of drinking but not characteristic of drunkenness.

The curves showing the incidence of gait and speech abnormalities paralleled each other and followed closely the incidence of clinical intoxication. It might be supposed that the curve of gait abnormalities would approximate that of clinical intoxication be-

cause this criterion has been made essential for the diagnosis. The curve representing speech abnormality was similar to both gait abnormality and that of the incidence of clinical intoxication. Hence, it may be reasoned that both speech and gait abnormalities are characteristic not only of drinking but also of actual drunkenness.

That the differential diagnosis of acute alcoholism is difficult at times is evidenced by the 72 cases which at admission were alcohol-free, although a pre-admission diagnosis of acute alcoholism has been made. Particularly difficult is the diagnosis when the case is comatose. This was shown by the 32 cases, admitted in coma which were improperly diagnosed as due to alcohol. On the other hand, in such cases the possibility of alcohol being the etiologic agent must always be borne in mind. One such case may be used as an example. The police requested admission for a white male who was found lying unconscious in the street. After artificial respiration had been administered by the fire department, the patient was brought to the hospital with a diagnosis of heat stroke. At admission the possibility of alcoholic coma was suspected. The alcoholic concentration of the blood was 0.37%.

The correlation of acute alcoholism and the blood alcoholic concentration becomes valid only if the concentration of blood and brain alcohol shows a constant relationship. Experimental work in dogs by Harger *et al.*² in 1937 has shown that a constant relationship between blood and brain alcohol does exist at all periods up to 12 hours following ingestion of alcohol. No similar data have been submitted concerning a possible relationship to brain and urine alcohol.

In 372 cases in which both blood and urine examinations were available on the same patient the alcohol concentration of the urine was either equal to or higher than the concentration of alcohol in the blood. The average was blood to urine as 1 to 1.32. The reason for higher concentration of alcohol in the urine is not altogether clear.

In comparing the blood and urine determinations it is seen that the incidence of clinical intoxication is quite similar. Its incidence at groups 0.15 to 0.30% alcohol is somewhat lower in the urine than in the blood at similar levels. This lag is to be expected because of the ratio of alcohol in blood and urine already mentioned. At any rate, intoxication was found in all cases in both blood and urine in the group 0.45% alcohol. Because of the unpredictable ratio between blood and urine alcohol, a like situation is to be expected in a comparison between brain and urine alcohol. Therefore, the alcoholic content of the urine does not afford an altogether reliable indicator of the status of the other body tissues. It was noted, however, that while the ratio between urine and blood alcohol showed considerable variations at low concentrations of alcohol, at higher concentrations the ratio approached unity. The slight decrease in intoxication noted at group 0.40% alcohol in the blood

may be explained by the relatively small number of cases occurring at this level and is without significance.

Our findings as to the incidence of intoxication at various levels of alcoholic concentration correlate well, on the whole, with those of other studies. However, it was not until the concentration bracket of 0.45% alcohol in both blood and urine was reached that all patients were clinically intoxicated. This is in contradistinction to the findings of previous workers, who observed intoxication in 100% of cases at concentrations of 0.20 to 0.30% alcohol. The striking rise in the incidence of inebriation at levels of from 0.10 to 0.20% alcohol noted by Hoffman,⁵ Widmark¹¹ and Schwarz,⁹ and also by the smaller series of Bogen¹ and Harger,³ are duplicated in this series.

There is no case in this series with a concentration above 0.50% alcohol in either blood or urine. Two deaths have occurred at 0.47 and 0.48% alcohol in the blood. When it is realized that at 0.40% alcohol, a concentration close to the lethal point, that an individual may show so little effects as to be adjudged sober by our criteria, or, on the other hand, that he may be in coma at this same level, it becomes evident that there exists a marked variation in the individual's reaction to alcohol. This variation may perhaps be explained by tolerance of the body cells to alcohol as in this paper only definite concentrations of alcohol have been considered and not the amount of alcoholic beverage consumed in attaining a given concentration. Newman⁸ has shown that a tolerance may be produced in dogs by making them "chronic alcoholic" from the daily ingestion of large quantities of alcohol. These animals exhibited less effects from a given concentration of alcohol in the blood than did normal dogs brought to the same concentration. Most of the cases in this series were presumably chronic alcoholics and would be expected to show a tolerance to alcohol as compared to the neophyte or occasional drinker. While most cases were drunk at concentrations of 0.35% alcohol, we have had 1 case unaffected by a concentration of 0.40% alcohol as already stated. Hence, the limit of tolerance might be placed at 0.45% alcohol. On the other hand, intoxication in the occasional drinker occurs at considerably lower concentrations since the experimental feeding of alcohol to this type of individual² has resulted in intoxication, according to our standards, at concentrations as low as 0.075% alcohol.

Summary. 1. A correlation was made of the clinical findings and the content of alcohol in the blood of 1150 cases admitted to the Buffalo City Hospital with a pre-admission diagnosis of acute alcoholism. Alcohol was found in the blood of 1000 cases. In 372 of these cases, the urine was also obtained. A total of 381 urines, all showing alcohol, were examined.

2. Of the 1000 cases with alcohol in the blood, 779 (77.9%) were found in the concentration groups of 0.15 to 0.30% alcohol inclusive.

Of the 381 cases in which the urine was examined, 266 (70%) fell in concentration brackets of 0.20 to 0.35% alcohol inclusive.

3. Employing the criteria for the diagnosis of acute alcoholic intoxication as outlined, clinical intoxication was found in the blood series in approximately 10% of the cases at the concentration group of 0.05% alcohol; in 18% at 0.10% alcohol; 47% at 0.15% alcohol; 83% at 0.20% alcohol; 90% at 0.25% alcohol; and 95% at 0.30% alcohol. Intoxication was present in 100% of cases in the concentration group of 0.45% alcohol. No cases were observed above 0.50% alcohol in either blood or urine.

4. Incidence of clinical intoxication in the urine series approximated that found in the blood series, although in general a lag was noted, most marked at concentrations of 0.15 to 0.30% alcohol. Intoxication was found in all cases at 0.45% alcohol.

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STUDIES IN ALCOHOL.

II. EXPERIMENTAL FEEDING OF ALCOHOL TO NON-ALCOHOLIC INDIVIDUALS.

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AN attempt has been made to correlate the clinical manifestations of acute clinical intoxication occurring when known amounts of alcohol were fed with the various blood alcoholic concentrations so obtained. A review of the literature has revealed no studies of an exactly similar nature.

Method. Ethyl alcohol, in concentrations of approximately 10%, was fed to 20 young normal adults, in 4 groups of 5 members each. All were either occasional drinkers or, in a few instances, total abstainers. Group 1 received 1 cc. per kg. of body weight; Group 2, 1.25 cc.; Group 3, 1.5 cc.; and Group 4, 2 cc. Ingestion was begun in the morning on a fasting stomach or after a light breakfast and was completed in 45 minutes or less. Samples of blood from the median basilic vein were taken regularly at 1-, 2-, 3-, 4-, 6-, 8-, 12- and 24-hour intervals, the first sample being taken

exactly 1 hour after the first drink. The blood alcohol content was determined by the method devised by Heise.² In addition, the individuals were examined for acute alcoholic intoxication using the clinical criteria as previously outlined.³

Results. Graphs 1, 2, 3 and 4 show the concentration of alcohol in the blood of each of the members of the four groups at the various time intervals. In all cases, the highest concentration occurred 2 hours after the beginning of ingestion and was 0.10, 0.13, 0.15 and 0.19% alcohol respectively in the four groups. In all four groups, the concentration of alcohol fell somewhat abruptly from the second to the sixth hour after ingestion, after which it then decreased more gradually. In all cases in Groups 1 and 2, the blood was alcohol-free in 8 and 12 hours respectively, whereas in Groups 3 and 4, the blood was alcohol-free in 24 hours.

TABLE 1.—ALCOHOL, 1 CC. PER KG. BODY WEIGHT.
(Group 1.)

Case No.:	1.	2.	3.	4.	5.
Alcoholic odor . . .	+	+	+	+	+
Flushed face . . .	+	+	+	+	+
Dilated pupils . . .	+	0	+	0	+
Speech abnormalities . .	+	0	0	+	0
Gait abnormalities . .	+	+	0	0	0
Intoxicated . . .	Yes	Yes	No	No	No

TABLE 2.—ALCOHOL, 1.25 CC. PER KG. BODY WEIGHT.
(Group 2.)

Case No.:	6.	7.	8.	9.	10.
Alcoholic odor . . .	+	+	+	+	+
Flushed face . . .	+	+	+	0	+
Dilated pupils . . .	0	0	+	+	+
Speech abnormality . .	+	+	+	0	0
Gait abnormality . .	0	+	+	+	+
Intoxicated . . .	No	Yes	Yes	Yes	Yes

TABLE 3.—ALCOHOL, 1.5 CC. PER KG. BODY WEIGHT.
(Group 3.)

Case No.:	11.	12.	13.	14.	15.
Alcoholic odor . . .	+	+	+	+	+
Flushed face . . .	+	+	+	0	+
Dilated pupils . . .	0	0	0	+	+
Slurred speech . . .	0	+	0	0	0
Gait abnormality . .	0	+	+	0	0
Intoxicated . . .	No	Yes	Yes	No	No

TABLE 4.—ALCOHOL, 2 CC. PER KG. BODY WEIGHT.
(Group 4.)

Case No.:	16.	17.	18.	19.	20.
Alcoholic odor . . .	+	+	+	+	+
Flushed face . . .	0	0	+	0	0
Dilated pupils . . .	0	+	0	+	+
Slurred speech . . .	+	+	+	+	+
Gait abnormality . .	+	+	+	+	+
Intoxicated . . .	Yes	Yes	Yes	Yes	Yes

All 20 cases were examined for evidence of clinical intoxication. Tables 1, 2, 3 and 4 show the incidence of the 5 clinical criteria and

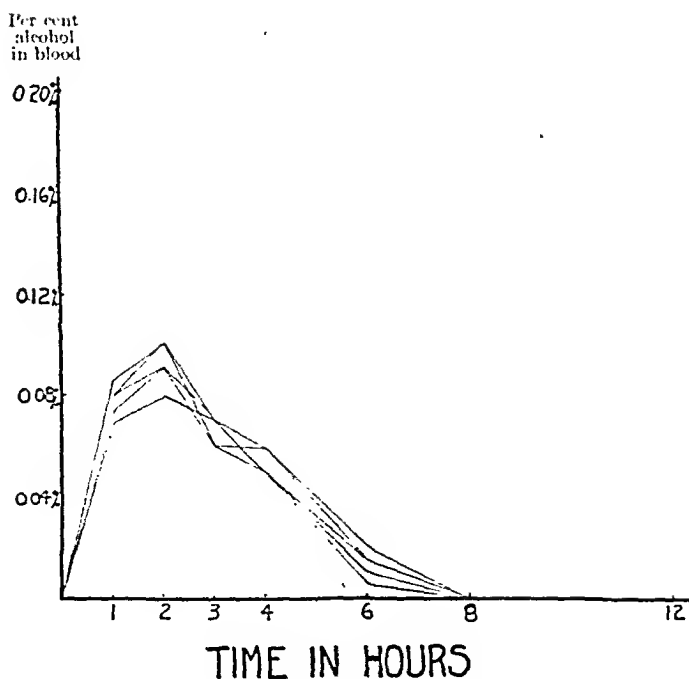
of clinical intoxication in all members of the groups. All cases showed an alcoholic odor to the breath and in 14 cases a flushed face was present. Dilated pupils and slurred speech occurred in 11 cases, while gross reeling, swaying, or staggering was found in 13 cases. Using the clinical criteria for intoxication as described previously, a diagnosis of acute alcoholism was made in 13 cases, or an incidence of 65%. In general, the greatest degree of intoxication in any given case was noted when the concentration of alcohol was highest in the blood stream, namely 2 hours after ingestion. In the intoxicated cases, all 5 criteria were found in 2 cases; 4 criteria were present in 7 cases, while in 4 cases only 3 criteria were noted. Of the 7 non-intoxicated, in none of whom a gait abnormality was found, 4 cases exhibited 3 of the other 4 criteria while the other 3 cases had but 2 present. In addition, all exhibited evidence of mental instability, talkativeness, excitability and lack of self-control.

Two cases of Group 1 became intoxicated at concentrations of blood alcohol of 0.09 and 0.10% alcohol. Four of the 5 persons in Group 2 were drunk at concentrations of 0.075, 0.11 and 0.13% (2 cases). Only 2 of 5 cases in Group 3 became inebriated, both at 0.15% alcohol. All 5 cases of Group 4 were intoxicated at concentrations of 0.18 and 0.19%.

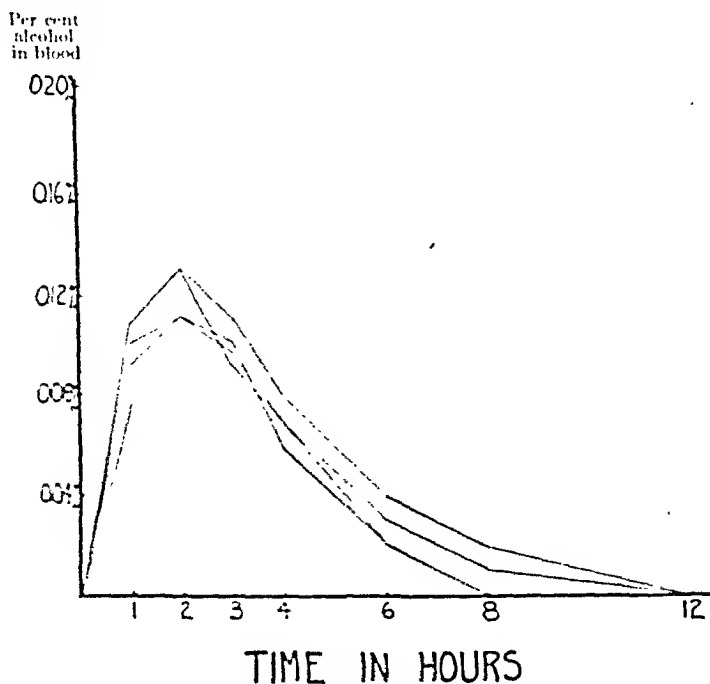
TABLE 5.—INCIDENCE OF ACUTE CLINICAL INTOXICATION AT DEFINITE GROUPS OF BLOOD ALCOHOL CONCENTRATION—COMPARISON OF EXPERIMENTAL AND HOSPITAL GROUPS.

Concentration of alcohol.	Experimental.			Hospital.		
	No. of cases.	No. of cases intoxicated.	Percent-age cases intoxicated.	No. of cases.	No. of cases intoxicated.	Percent-age cases intoxicated.
0.075-0.125% . . .	8	4	50	87	16	18
0.125-0.175% . . .	7	4	57	132	61	47
0.175-0.225% . . .	5	5	100	330	276	83

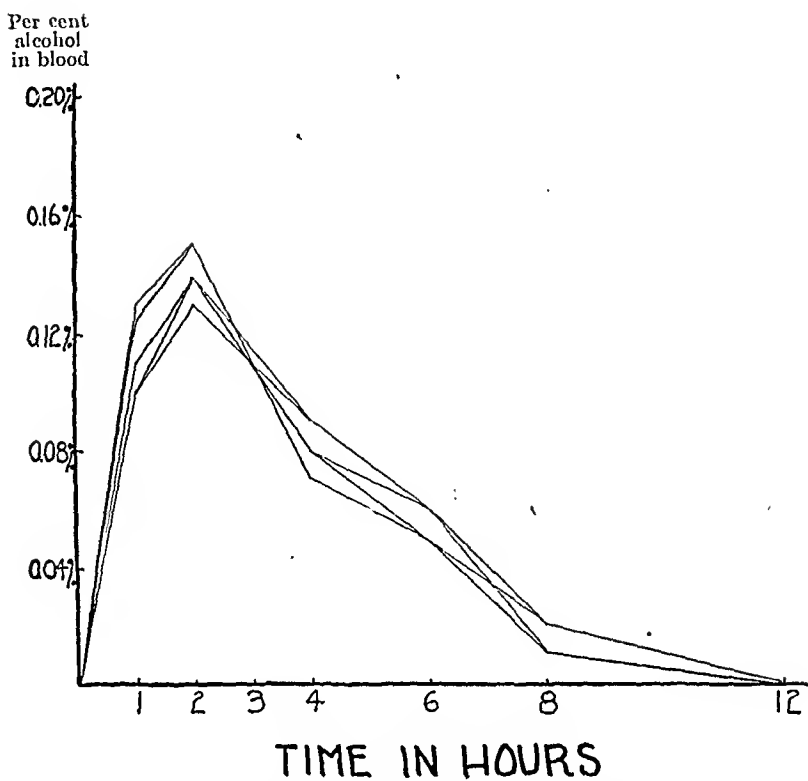
Discussion. The incidence of clinical intoxication at definite groups of alcoholic concentration in the blood in this series is compared to that in the larger group as shown in Table 5. The more frequent occurrence of clinical intoxication (50%) at relatively low concentrations of alcohol in the blood (0.075 to 0.125%), found in these studies is in contrast to the lower incidence of the condition noted at similar concentrations in the larger group, namely 18%. Such a difference may be significant in spite of the great disproportion in the number of cases in the two groups. It may be supposed that the chief variance of these two groups depends upon their alcoholic habits. Members of the groups which were fed alcohol were occasional or non-drinkers, whereas those of the larger group were, for the most part, chronic alcoholics, the majority having known alcoholic histories of long standing. Thus, it would appear logical to explain the variation in their reaction to alcohol on the basis of an acquired tolerance, a status which has been shown to



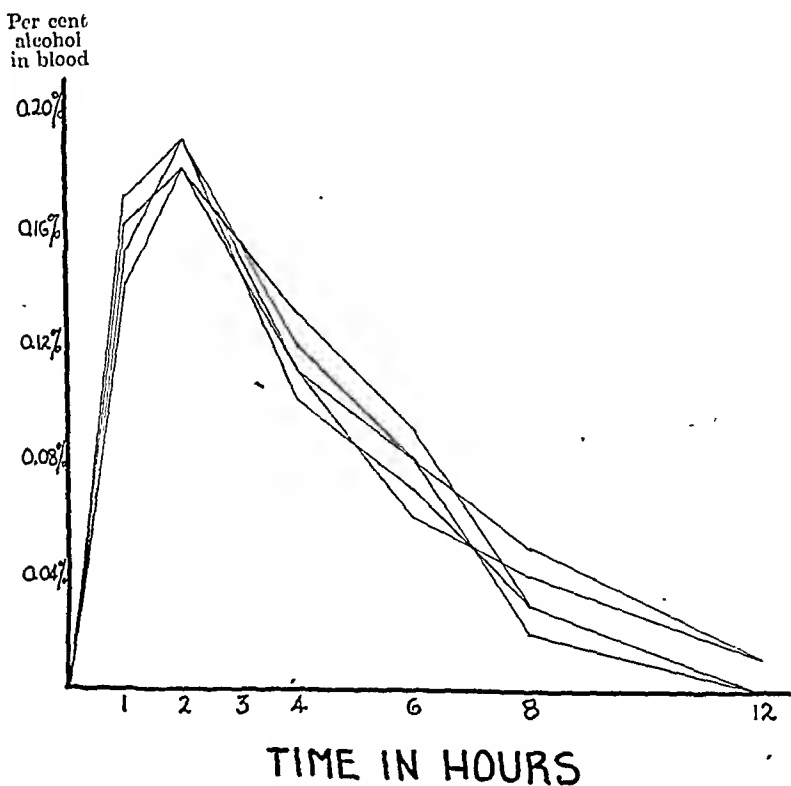
GRAPH 1.—Experimental feeding; alcohol, 1.0 cc./kg. body weight. Group I.



GRAPH 2.—Experimental feeding; alcohol, 1.25 cc. kg. body weight. Group II.



GRAPH 3.—Experimental feeding; alcohol, 1.5 cc./kg. body weight, Group III.



GRAPH 4.—Experimental feeding; alcohol, 2 cc./kg. body weight, Group IV.

exist in experimental animals by Newman.⁴ In addition, it appears that the occasional drinker may possess some tolerance in comparison to the non-drinker. Four non-drinkers were intoxicated at levels of 0.075 to 0.11% alcohol while 3 cases, occasional drinkers, were not intoxicated at 0.14 and 0.15% alcohol.

It has been noted that all chemical data have been tabulated in terms of percentage of alcohol by weight per 100 cc. of blood. In order to convert to alcohol per 100 gm. of blood, the concentration of alcohol must be multiplied by $\frac{1.00}{1.06}$ as the specific gravity of human blood is 1.06. Since the specific gravity of ethyl alcohol is 0.79, 1 cc. of alcohol weighs only 0.79 gm. It will be seen that when 1 cc. of alcohol is fed per kg. of body weight, the maximum concentration of alcohol which could be attained, assuming that complete absorption and uniform diffusion of alcohol throughout the body tissues has occurred, could be no higher than 0.079% alcohol by weight per 100 gm. of tissue. Actually at 2 hours, concentrations in the blood as high as 0.10% alcohol (per 100 cc. blood) were found. This percentage, calculated to 100 gm. blood, would be lowered to 0.094%, which is still above the highest possible theoretical value. This variation between the calculated and determined values indirectly confirms the experimental work of Harger,¹ who has recently shown that there is a lag in the diffusion of alcohol in skeletal muscle until 3 hours after ingestion, diffusion being uniform after that time. In addition, the initial sharp rise in the concentration of blood alcohol following ingestion, the peak of which is reached 2 hours after ingestion, and the subsequent rapid fall is explained by this so-called muscle lag.

It has been shown in Graphs 1, 2, 3 and 4 that when 1, 1.25, 1.5 and 2 cc. of ethyl alcohol are fed per kg. of body weight, the percentage of alcohol by weight per 100 cc. of blood approximates at 2 hours, 0.10, 0.125, 0.15 and 0.20% respectively. It would seem, therefore, that in order to calculate the smallest amount of alcohol ingested necessary to produce a given concentration of alcohol in the blood, a basis of cc./kg. rather than gm./kg. be used. After a period of 3 hours the muscle lag need not be considered, at that time calculations might be made on a basis of gm./kg. It is assumed in such calculations that all alcohol be consumed in an hour or less on a relatively empty stomach in a concentration of 10%. Whether the above assumptions under the same conditions hold true for the chronic alcoholic is rather doubtful. Jungnickel, Schmidt, Fleming and Stotz, Bernhard and Goldberg (quoted by Newman) and Newman and Card⁴ have shown that the concentration of alcohol in the blood is slightly higher in chronic alcoholics than in the non-alcoholics when the same amounts of alcohol are fed.

From the work of Harger, which as yet has not been confirmed, it would appear that all tissues except skeletal muscle show an

immediate and constant diffusion of alcohol, although this ratio may not always be unity. The most important relationship, that of blood to brain, appears to be constant at all times regardless of the time after the ingestion of alcohol. It follows, then, that the concentration of alcohol in the brain may be predicted if the concentration in the blood is known. Since intoxication is dependant upon the concentration of alcohol in the central nervous system, it would seem logical, therefore, to predicate intoxication on a determination of the alcohol content of the blood. Harger's work, however, was performed on non-alcoholic animals. Whether the constant relationship between blood and brain alcohol exists in chronic alcoholics is as yet undetermined.

Conclusions. 1. The blood alcohol content was determined in 20 normal volunteers at regular intervals following the ingestion of 1, 1.25, 1.5 and 2 cc. of alcohol per kg. of body weight.

2. Acute clinical intoxication occurred in 50% of cases in which the alcohol concentration in the blood varied from 0.075 to 0.125%; in 57% in concentrations from 0.125 to 0.175%; and in 100% in concentrations from 0.175 to 0.225% alcohol.

3. The incidence of acute clinical intoxication in these so-called normal individuals at low alcoholic concentrations was much higher than was the incidence at similar concentrations in a larger group consisting primarily of chronic alcoholics.

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THE RED CELL MASS IN POLYCYTHEMIA IN RELATION TO DIAGNOSIS AND TREATMENT.

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POLYCYTHEMIA vera is primarily an increase in the number of erythrocytes. This increase is the only constant abnormality in the disease and is responsible for the symptoms and physical findings. The spleen enlarges in storing and disposing of some of the excess red cells; the cyanosis depends on the slow circulatory rate resulting from the high viscosity. The treatment of polycythemia is based on disposing of the excess of red cells by hemolysis or bleeding. The diagnosis and treatment thus require accurate data concerning the erythrocytes.

The red cells per unit volume of blood are always increased in polycythemia vera. An increase is also observed, however, in symptomatic polycythemia due to an interference with oxygenation

of hemoglobin, so a diagnosis of polycythemia vera cannot be made on an increased number of cells per cubic millimeter alone. The blood volume is a valuable aid in differentiating the symptomatic and idiopathic types. In symptomatic polycythemia the blood volume is seldom increased; in polycythemia vera the blood volume is always increased. Very little emphasis has been placed on this characteristic increase in blood volume in polycythemia vera even in such complete reviews as those of Harrop¹ and Parkes-Weber and Bode.² Blood-volume determinations in a few cases have been recorded over many years by a number of workers. The only large series is the 50 cases reported by Rowntree, Brown and Roth.³ The blood volume may be increased in a wide variety of clinical conditions, however, so an increase is not limited to polycythemia vera.

Method. In making the blood-volume determinations reported here-with, the colorimetric method of Rowntree, Brown and Roth,³ using Congo red (National Anilin, Schultz, No. 307), has been employed. A freshly made 1.5% solution of the dye is sterilized by bringing to the boiling point twice. The exact amount of solution delivered from the 18-cc. graduation mark on a 20-cc. record syringe has been determined and each patient is given this amount intravenously. Exactly 4 minutes after the dye is injected, blood is withdrawn from the other arm without the use of a tourniquet. A 1.4% solution of sodium oxalate is used as the anticoagulant for the hematocrit readings. The red cell mass is simply calculated from the hematocrit reading and the total blood volume.

The blood findings in 20 consecutive patients with polycythemia vera have been studied to determine the most significant indicator of changes in the red cells on which the disease depends. The data are recorded in Table 1. For comparison, the findings in a group of patients who presented either a high red cell count or an increased blood volume due to symptomatic polycythemia are shown in Table 2. The red cell count per cubic millimeter, the total blood volume, the total red cell mass, the total red cell count, and the blood volume and red cell mass per kilogram of body weight are greater than normal in every patient with polycythemia vera. In the symptomatic group, the red cell count per cubic millimeter, the total red cell count, the total blood volume, the total red cell mass, or the blood volume per kilogram may be increased but there is never a significant increase in the red cell mass per kilogram.

The data in the two groups have been analyzed with respect to the following possible indicators of variation in the red cells:

1. Red cell count per cubic millimeter which measures the number of cells per unit volume only.
2. Total red cell count, which depends on the number per unit volume and the total blood volume but does not recognize the mean cell volume.
3. Total blood volume, which measures both cells and plasma and varies with body weight.

TABLE 1.—BLOOD FINDINGS IN POLYCYTHEMIA VERA.

Number.	Wt. (kg.).	Red cell count per c.mm. (mil- lions).	Hemat- ocrit reading (vol. %).	Total volume.			Blood volume per kg. (cc.).	Red cell mass per kg. (cc.).	Total number red cells (tril- lions).
				Whole blood (cc.).	Plas- ma (cc.).	Red cell mass (cc.).			
Mean of 10 normals	56	4.50	40	<i>Female.</i>					
1	58	5.89	48	3702	2220	1482	66.4	26.4	16.7
2	58	5.44	47	5600	2912	2688	98.0	47.2	33.0
3	58	6.51	56	6090	3228	2862	105.0	49.3	33.1
4	82	6.60	60	5443	2558	2885	94.0	50.0	35.4
5	52	7.68	65	6082	2432	3650	74.0	43.6	40.1
6	58	10.60	67	6063	2122	3941	117.0	75.8	45.6
				7659	2068	5551	132.0	96.0	81.2
Mean of 10 normals	77	5.00	45.5	<i>Male.</i>					
7	75	6.09	51	4960	2634	2326	64.4	30.0	24.8
8	62	6.12	57	6319	3096	3223	84.3	43.0	38.5
9	75	7.10	63	5965	2365	3600	97.8	59.0	36.4
10	75	6.90	64	6811	2520	4291	90.0	56.0	48.4
11	80	7.22	62	7135	2568	4564	92.1	59.0	49.2
12	100	7.20	67	7590	2884	4706	95.0	59.0	54.8
13	74	9.25	61	7553	2492	5061	75.0	50.0	54.4
14	71	8.62	70	8836	3446	5400	119.0	72.9	81.7
15	64	8.33	73	8083	2425	5658	117.0	82.0	69.7
16	70	7.60	71	7768	2098	5670	121.0	88.6	66.5
17	58	7.66	72	8138	2360	5778	117.0	84.2	61.8
18	60	9.20	72	8025	2247	5778	138.0	100.0	61.5
19	80	7.90	70	8296	2323	5973	133.0	100.0	76.3
20	82	9.55	78	8557	2467	5990	107.0	74.0	66.6
				10454	2300	8154	127.5	100.0	100.8

TABLE 2.—BLOOD FINDINGS IN PATIENTS WITH HIGH RED CELL COUNT OR HIGH BLOOD VOLUME ONLY.

Number.	Weight (kg.).	Red cell count per c.mm. (millions).	Hematocrit read- ing (vol. %).	Total volume.			Blood volume per kg. (cc.).	Red cell mass per per kg. cc.	Total number red cells (trillions).	Diagnosis.
				Whole blood (cc.).	Plasma (cc.).	Red cell mass (cc.).				
Mean of 10 normals	56	4.50	40	3702	2220	1482	66.4	26.4	16.7	Normal
21	77	6.43	52	5040	2419	2621	65.0	33.8	31.4	
22	55	6.62	40	3728	2267	1461	68.0	26.0	23.1	
23	42	3.88	30	4156	2909	1247	100.1	29.7	16.1	
24	54	4.49	35	4781	3107	1674	88.0	31.0	21.5	
25	46	4.16	32	3881	2600	1281	84.4	27.9	16.1	Rheumatoid arthritis
										Hypertension; aortic insufficiency
										Rheumatoid arthritis
Mean of 10 normals	77	5.00	45.5	4960	2634	2326	64.4	30.0	24.8	Normal
26	79	6.07	50	5667	2833	2834	72.0	35.4	34.4	Obesity; dermatitis
27	132	6.15	55	6320	3223	3097	48.0	23.6	37.9	Obesity; angiospasm
28	84	6.23	48	5421	2819	2602	65.0	31.4	33.8	Obesity
29	59	4.20	40	5609	3365	2234	95.1	23.5	23.6	Multiple myeloma
30	56	3.19	33	6253	4189	2064	112.6	37.2	19.9	Rheumatoid arthritis

4. Total red cell mass, which recognizes all variants of the red cell only, number, total blood volume, hematocrit reading, and mean cell volume, but varies with body weight.

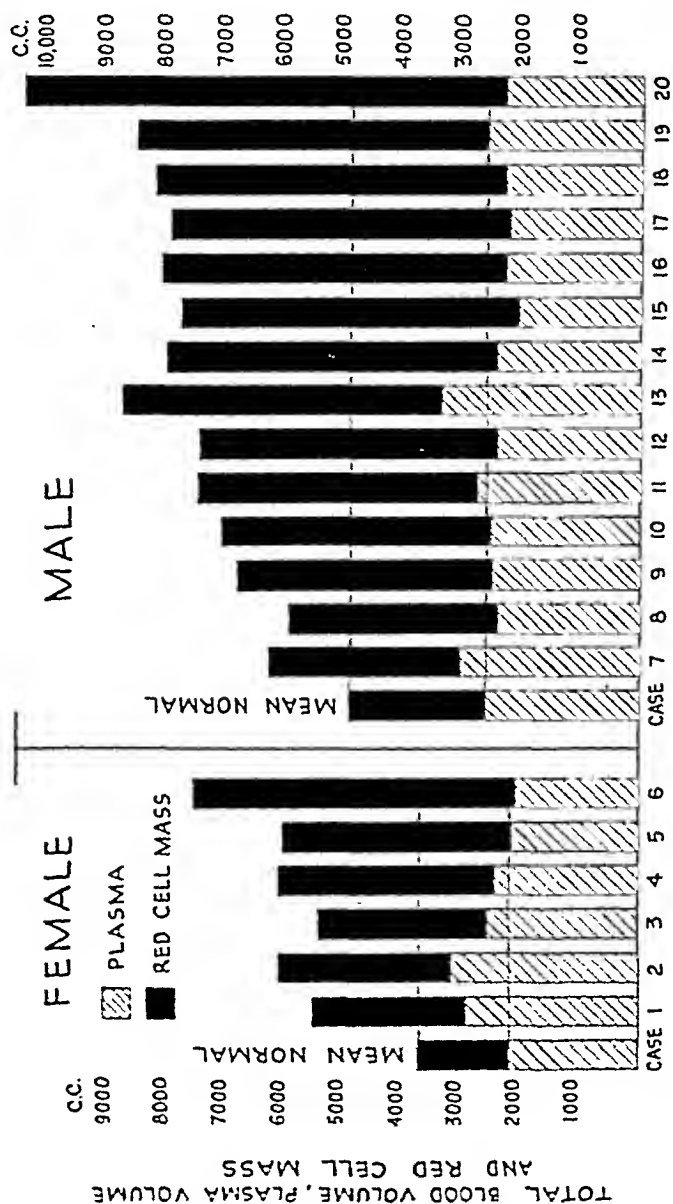


FIG. 1

5. Blood volume per kilogram, which measures both cells and plasma in relation to body weight.

6. Red cell mass per kilogram, which measures all variants of the red cell in relation to body weight.

The total blood volume, the plasma volume, and the total red cell mass for the 20 patients with polycythemia vera are shown in Figure 1 in relation to normal. The significant point here is the

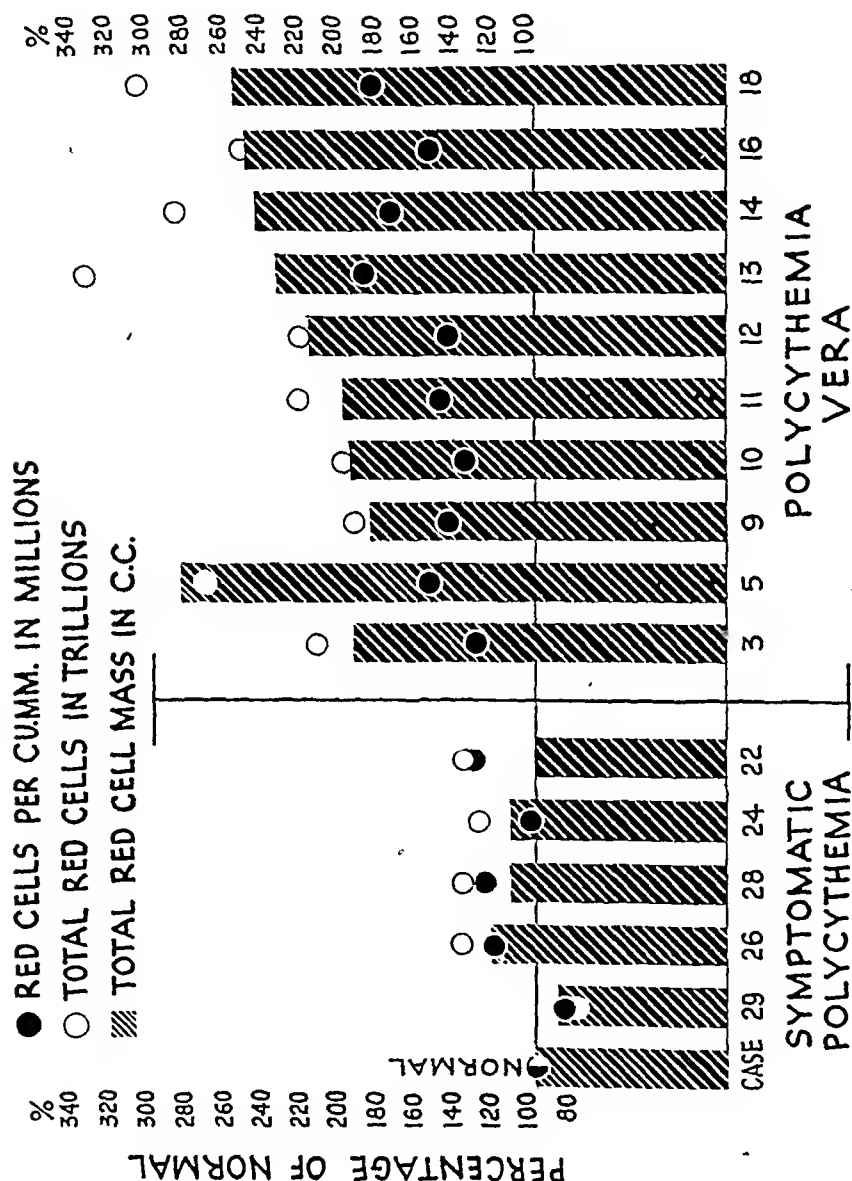


Fig. 2

remarkably little variation in plasma volume even with a great increase in total blood volume. The characteristic increase in blood volume is thus due almost entirely to an increase in cell mass. In Figure 2 the total red cell count, the red cell count per cubic millimeter, and the total red cell mass are compared. All data are figured in percentage relative to normal. In the idiopathic poly-

cythemia group, it is apparent the red cell count per cubic millimeter reflects very inadequately the total increase in red cells, since

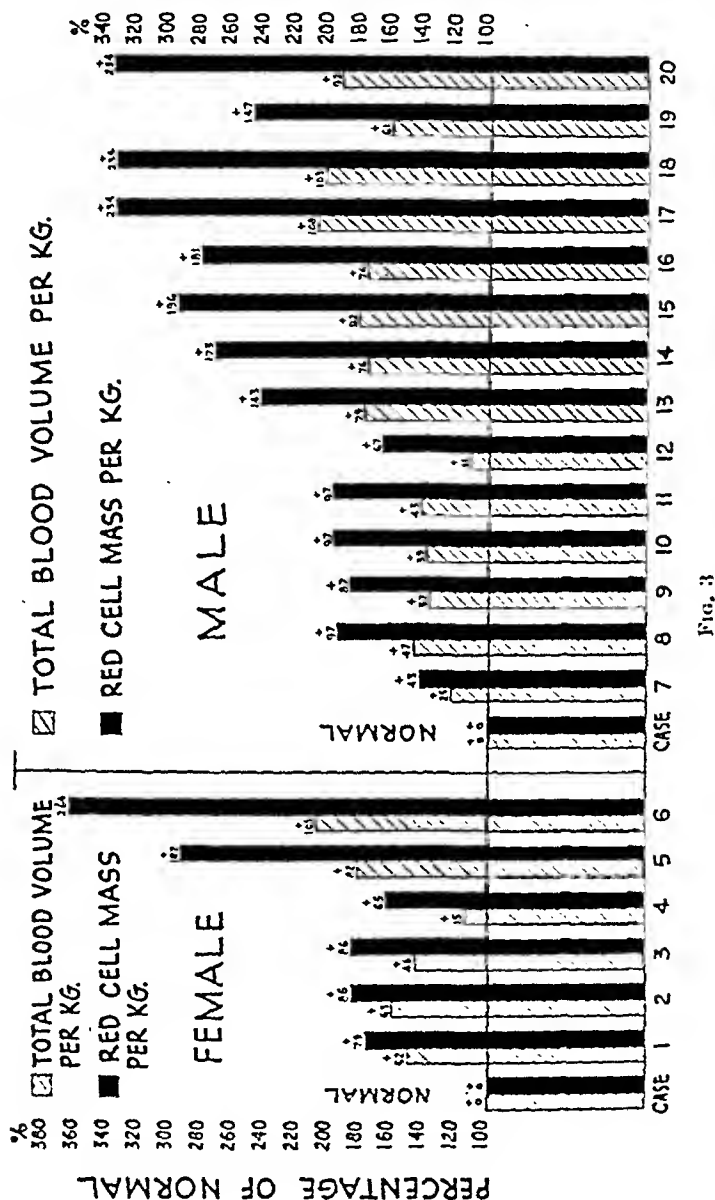


Fig. 3

the cell count is constantly much lower than the red cell mass. The total red cell count parallels more closely the variation in red cell mass but is usually relatively too high because the mean red

cell volume is frequently less than normal. In the cases of symptomatic polycythemia, the red cell mass is seldom significantly in-

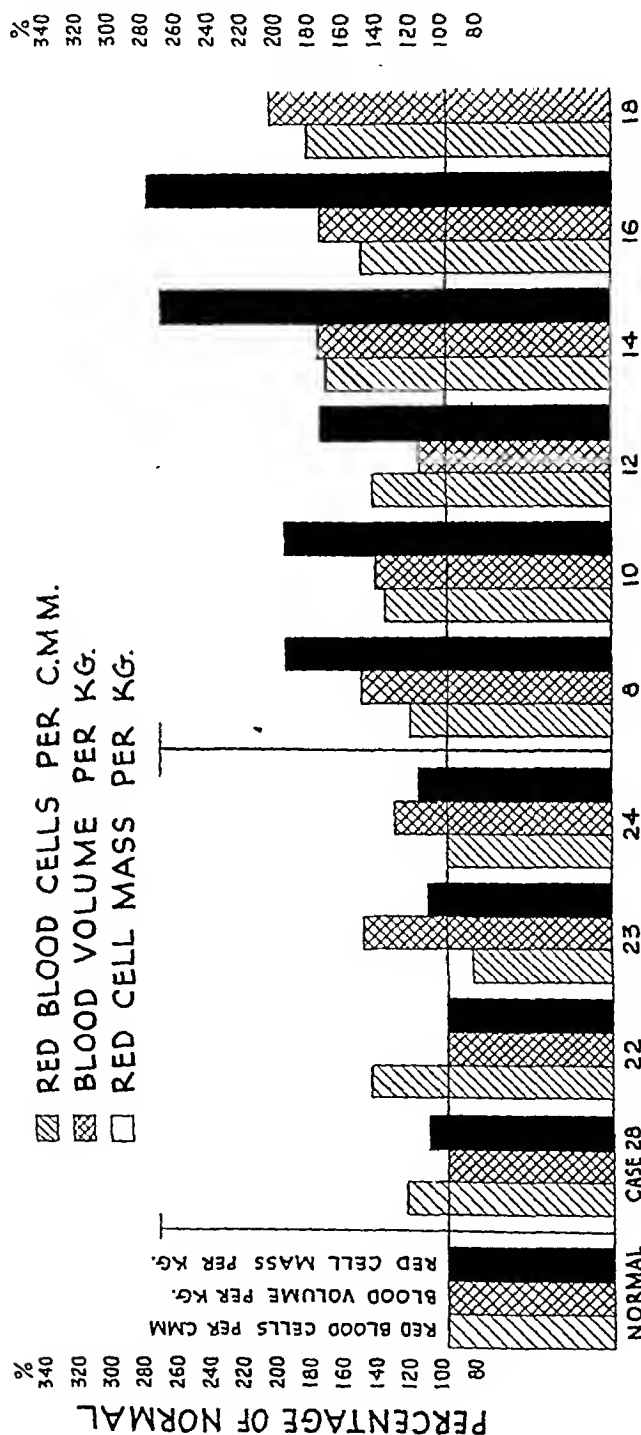


FIG. 4

creased, so here both the red cell count and total red cells are usually relatively too high.

In Figure 3 the total blood volume per kilogram and the red cell mass per kilogram are compared. Since the plasma volume is relatively constant, the percentage increase in red cell mass is very much greater than is the increase in total blood volume per kilogram.

In Figure 4 the red cell count per cubic millimeter and the blood volume and red cell mass per kilogram are compared in symptomatic polycythemia and polycythemia vera. In symptomatic polycythemia, the red cell mass per kilogram is not increased even with a high red cell count per cubic millimeter or a high blood volume per kilogram. If the blood volume is high, the blood volume per kilogram is higher than the red cell mass per kilogram. In polycythemia vera the red cell mass per kilogram is constantly high and relatively much higher than the red cell count per cubic millimeter or the blood volume per kilogram. It is apparent that the red cell mass per kilogram is: 1, the most sensitive and reliable indicator of total changes in the red cell in polycythemia; 2, constantly increased in polycythemia vera; and, 3, seldom increased in symptomatic polycythemia. The diagnosis of polycythemia vera is not justified without demonstrating such an increase.

TABLE 3.—POLYCYTHEMIA VERA—CHANGES IN RED CELLS IN RELATION TO TREATMENT.

No.	Wt. (kg.).	Date.	Red cell count per cmm. (milli- lions).	Hemat- ocrit read- ing (vol. %).	Total volume.			Blood volume per kg. (cc.).	Red cell mass per kg. (cc.).	Total number red cells (tril- lions).
					Whole blood (cc.).	Plas- ma (cc.).	Red cell mass (cc.).			
14	71	Normal for wt.	5.09	45	4572	2442	2130	64.4	30.0	22.85
	71	12-30-32	8.62	63	8953	2525	5558	117	78.3	75.86
	70	10- 5-37	7.90	60	7712	3055	4627	110	66.1	69.99
	72	11- 5-37	6.30	50	6916	3358	3358	93	49.4	43.57
	72	11-18-37	6.12	49	6449	3259	3160	90	44.0	39.47
	72	12- 6-37	6.54	53	6236	2931	3205	87	46.0	42.76
	72	1-17-38	5.82	49	6837	3487	3360	95	46.7	39.79
	76	2-23-38	6.18	50	6118	3059	3059	81	42.5	38.24
	76	3-17-38	6.15	49	5790	2953	2837	76	37.0	35.60

In treating polycythemia vera, the excess of red cells must be destroyed by hemolysis or removed by venesection. If a hemolytic agent such as phenylhydrazine or acetylphenylhydrazine is employed, the amount of drug tolerated depends on the relative mass of the red cell as the hemolytic reaction is a quantitative one. Since the red cell count does not show the relative mass of red cells, this cannot be depended on as a guide in treatment. Here the most desirable measure is the total red cell mass as shown for one patient in Figure 5. The data for this patient are recorded in Table 3. The normal red cell mass for each patient is calculated and an

attempt made to keep the red cells at this level by appropriate treatment.

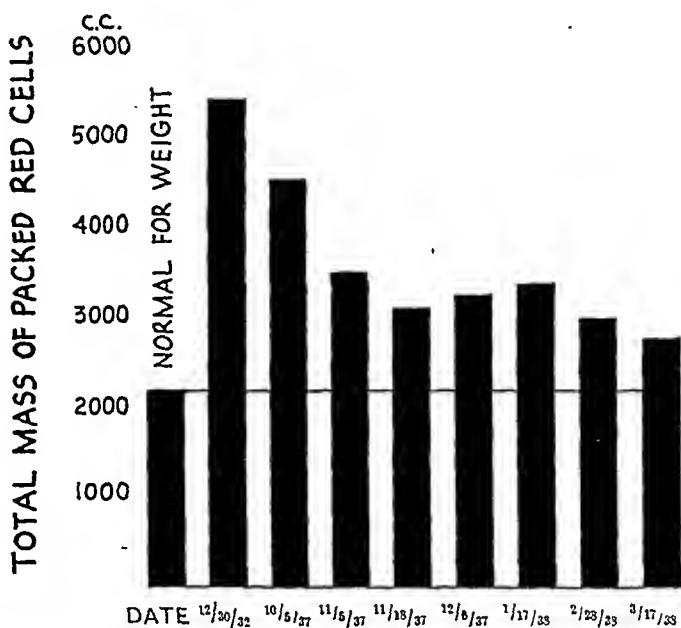


FIG. 5

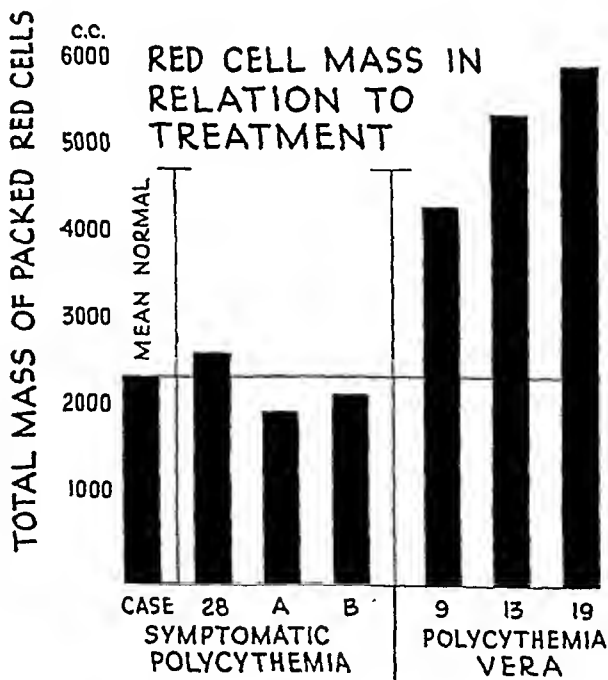


FIG. 6

The disastrous results seen in treating some patients on the basis of the red cell count alone is explained by the great variation in

total red cell mass. The actual red cell mass in 3 patients in whom a marked anemia quickly developed following treatment with acetylphenylhydrazine is shown in Figure 6. These patients all had high red cell counts per cubic millimeter so polycythemia vera was suspected. In 1, the total red cell mass was determined before treatment was given; in 2 others, after the blood had returned to the normal level. In each instance, the total red cell mass was normal so there was no real excess of red cells to dispose of. It is thus easy to see why a small amount of drug produced such a marked anemia.

Conclusions. The total blood volume is constantly increased in polycythemia vera. The increase concerns the red cells almost entirely since the volume of plasma is seldom greater than normal.

The red cell count per cubic millimeter does not measure accurately the total increase in red cells as it is relatively too low. The total red cell count is usually relatively too high due to a decrease in mean cell volume.

The red cell mass per kilogram is the most sensitive indicator of changes in the red cells. The red cell mass is constantly high in polycythemia vera and not significantly changed in symptomatic polycythemia.

The treatment of polycythemia vera should be based on the total red cell mass.

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THE USE OF MAPHARSEN IN THE TREATMENT OF MALARIA.

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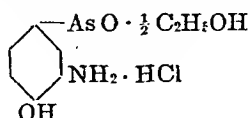
THE use of arsphenamines in the treatment of malaria was introduced almost as soon as their therapeutic efficacy in syphilis and spirochetal diseases was demonstrated. Werner^{1a,b} in 1910 described in detail the effect of intravenous and intramuscular injections of salvarsan (606) in tertian and estivo-autumnal malaria. He found that a single injection of 0.6 gm. caused disappearance of the parasites within 24 hours in almost all cases of tertian malaria and he found no recidives within several weeks. In estivo-autumnal malaria only half the cases responded favorably immediately after the injection and most of these recurred after several days. Since that time there have been innumerable publications on the use of salvarsan, neosalvarsan and other arsenated benzene compounds in malaria.

In some institutions, where therapeutic malaria is used extensively, neosalvarsan has been used to terminate the malaria chills and fever.

In the author's experience at least half of these cases would recur if only a single injection of neosalvarsan were given without the additional use of quinine or atabrine.

The introduction of mapharsen in treatment of syphilis naturally suggests its use in protozoan infections, particularly since the assay of the therapeutic efficacy of the drug is made in rat trypanosomiasis. For these reasons the use of mapharsen in treatment of therapeutic malaria was begun early in 1937. A fortunate opportunity also presented itself for its use in the naturally occurring disease in a case of chronic recurring malaria of about 8 months' standing.

Mapharsen is a trivalent arsenical which is exceedingly toxic and potent and is thought to be the effective breakdown product of the arsphenamines in the body. Chemically, it is meta-amino parahydroxy phenyl arsine oxide.²



Its toxicity and therapeutic index have been thoroughly studied by Tatum and Cooper³ and others. Its chief advantage seems to be constancy of chemical composition and as a result of this a relatively unvarying therapeutic index. Besides this the therapeutic dose is only one-tenth as great as the average dose of neoarsphenamine and consequently contains proportionately less arsenic.

The use of mapharsen in human syphilis has been thoroughly studied by Foerster and his coworkers¹ and by Gruhzt.² Since these original publications numerous authors have added data concerning the effectiveness of this drug. Its effectiveness in experimental trypanosomiasis is at least equivalent to that of the arsphenamines in the range of therapeutic dosage. A careful search of the literature reveals no reference to the use of mapharsen in the treatment of malaria previously. The present study deals with its effectiveness in this disease.

The technique of application of this remedy differs in no way from the administration in syphilis. According to the patient's weight 0.04 to 0.06 gm. are injected intravenously in the fasting state. Injections may be repeated at 5 to 7-day intervals. In most cases (over 90%), a single injection suffices to terminate the malaria permanently, but to insure against recurrences it is well to give 3 or 4 injections at the proper intervals (Table 1). In therapeutic malaria as usually used for dementia paralytica a course of 8 to 10 injections will usually be given for the sake of its antisiphilitic value and at the same time the malaria is permanently eradicated.

Mapharsen has been found to be much less toxic in debilitated patients than neoarsphenamine or even quinine. It seems likewise safer to use than atabrine. No toxic manifestations have been found in over 20 cases. Even malaria associated with severe leukopenia responded only favorably and with an increase in the leukocytes.

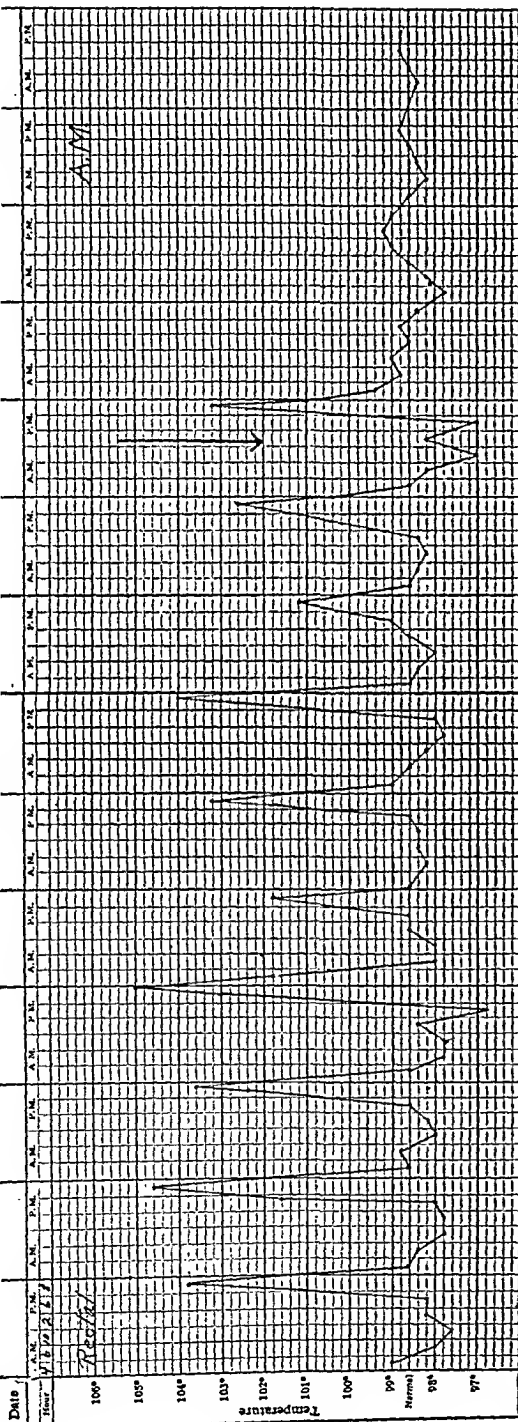


FIG. 1

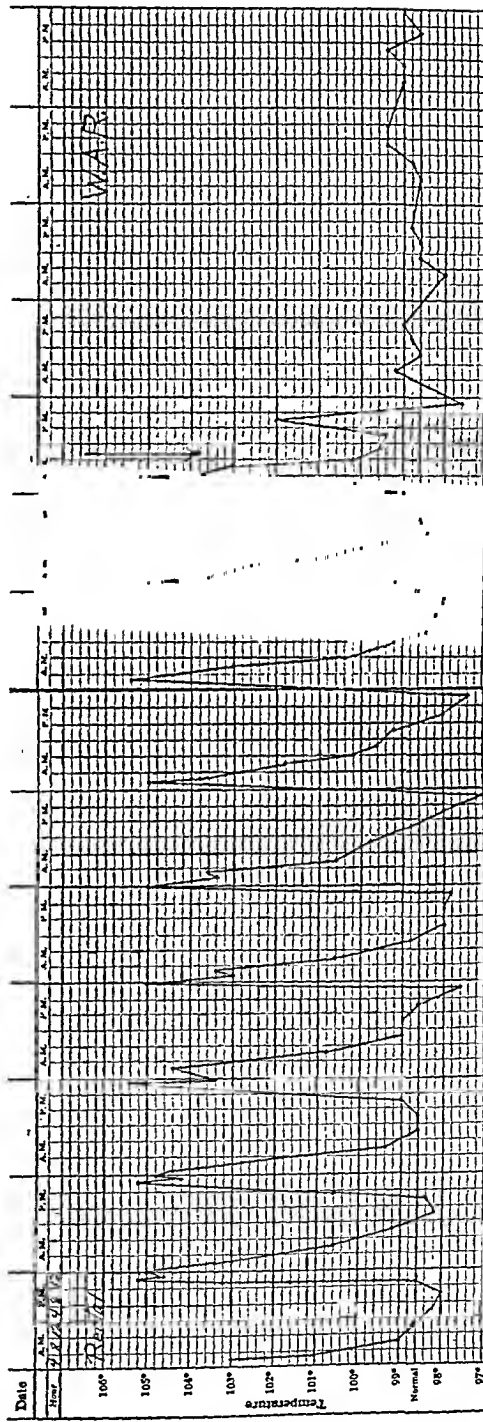


FIG. 2

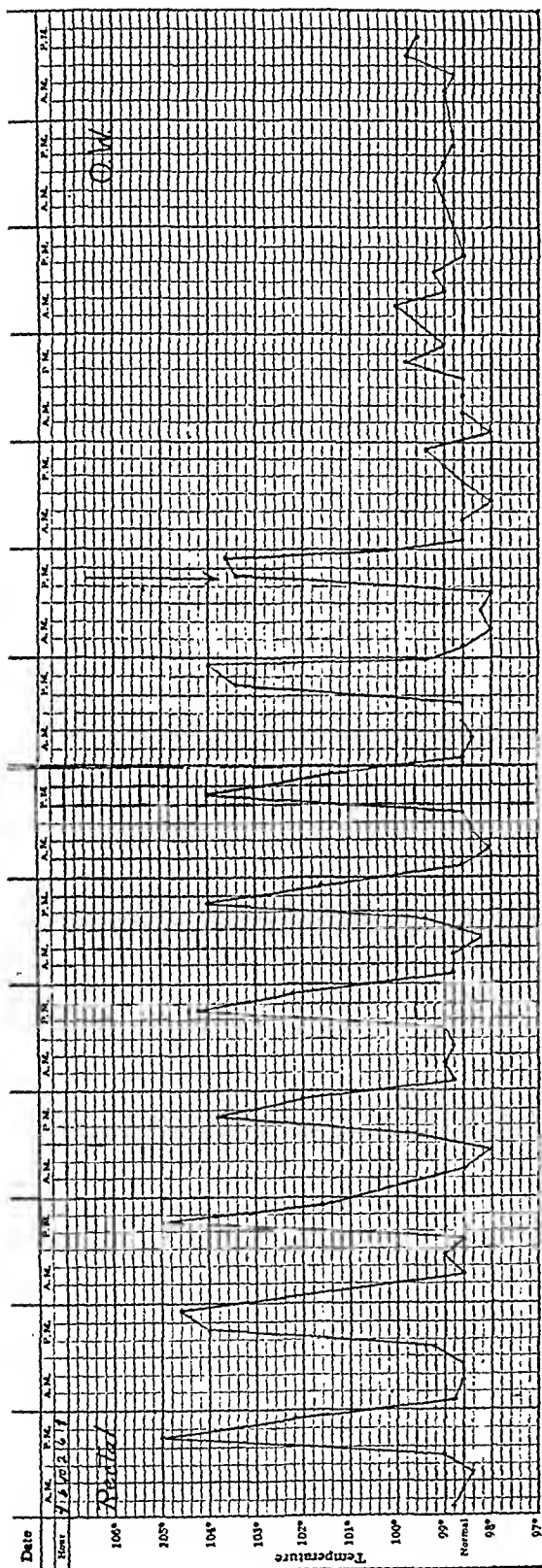


FIG. 3

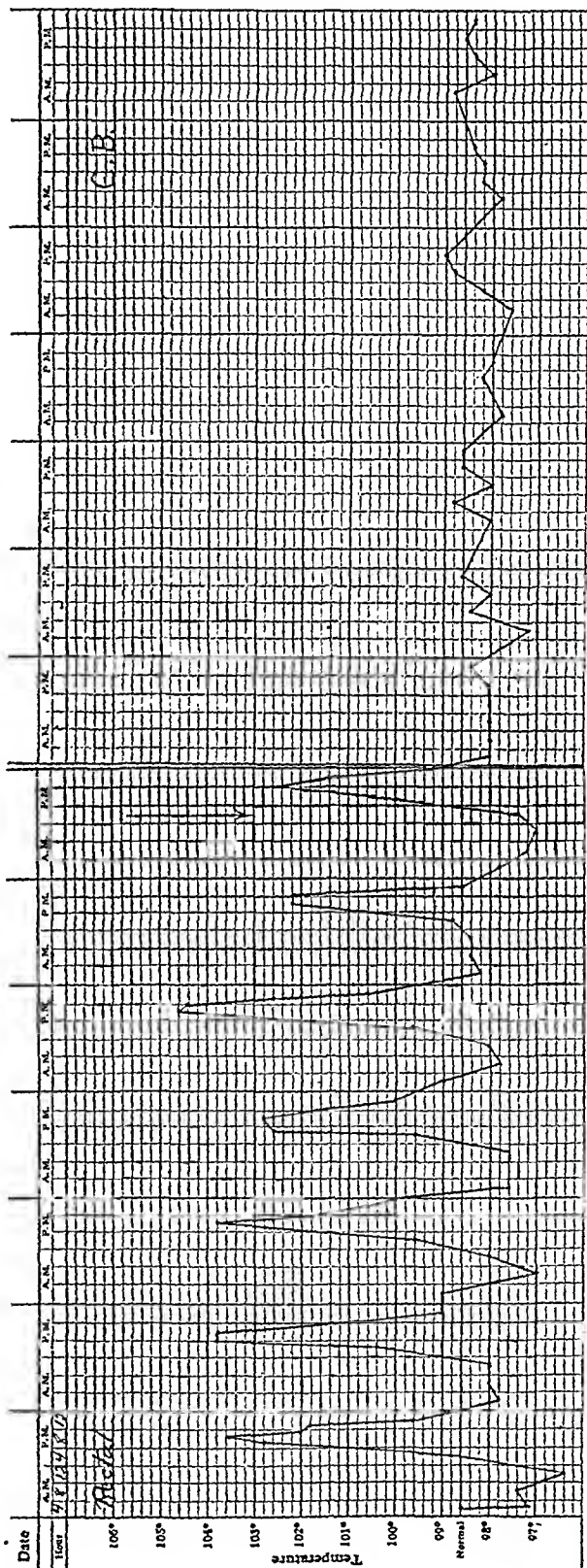


FIG. 4

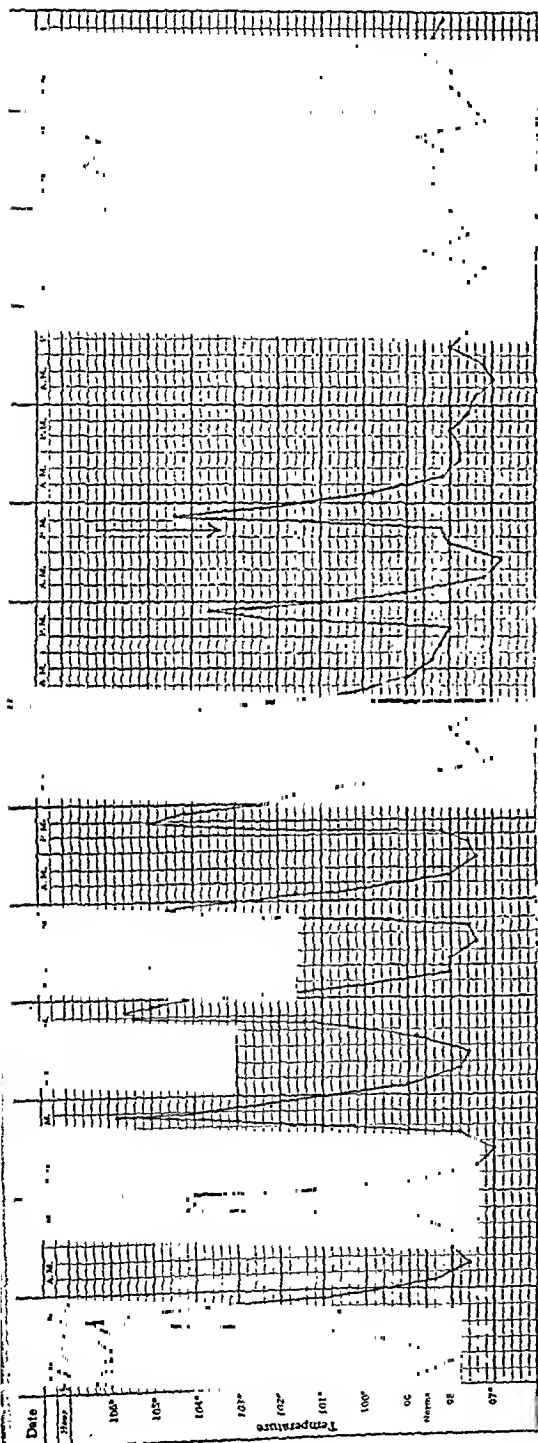


FIG. 5

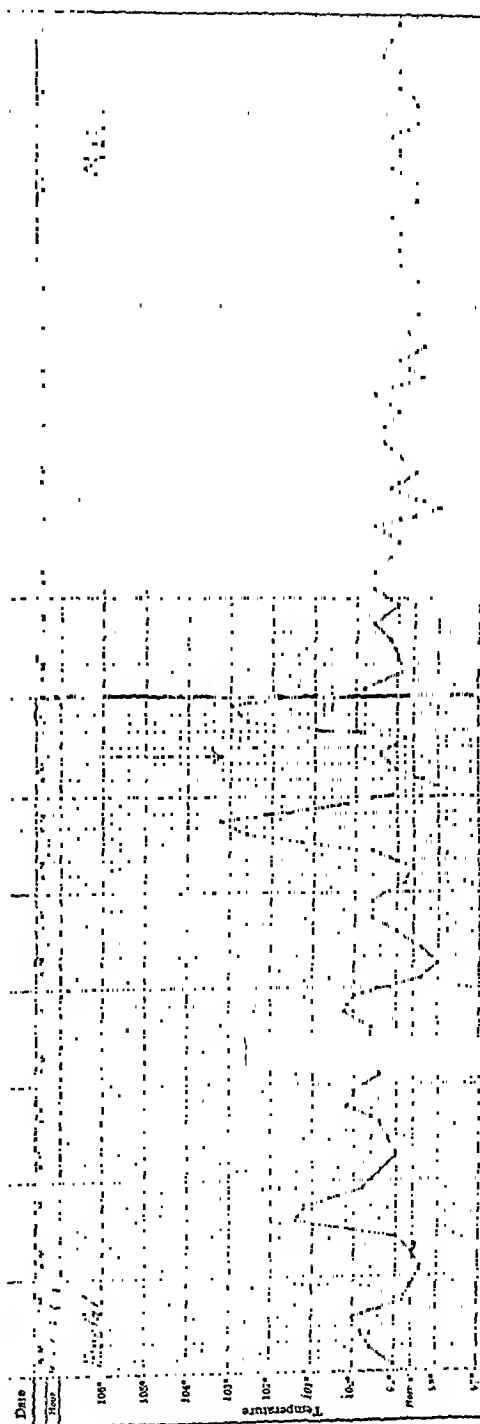


FIG. 6

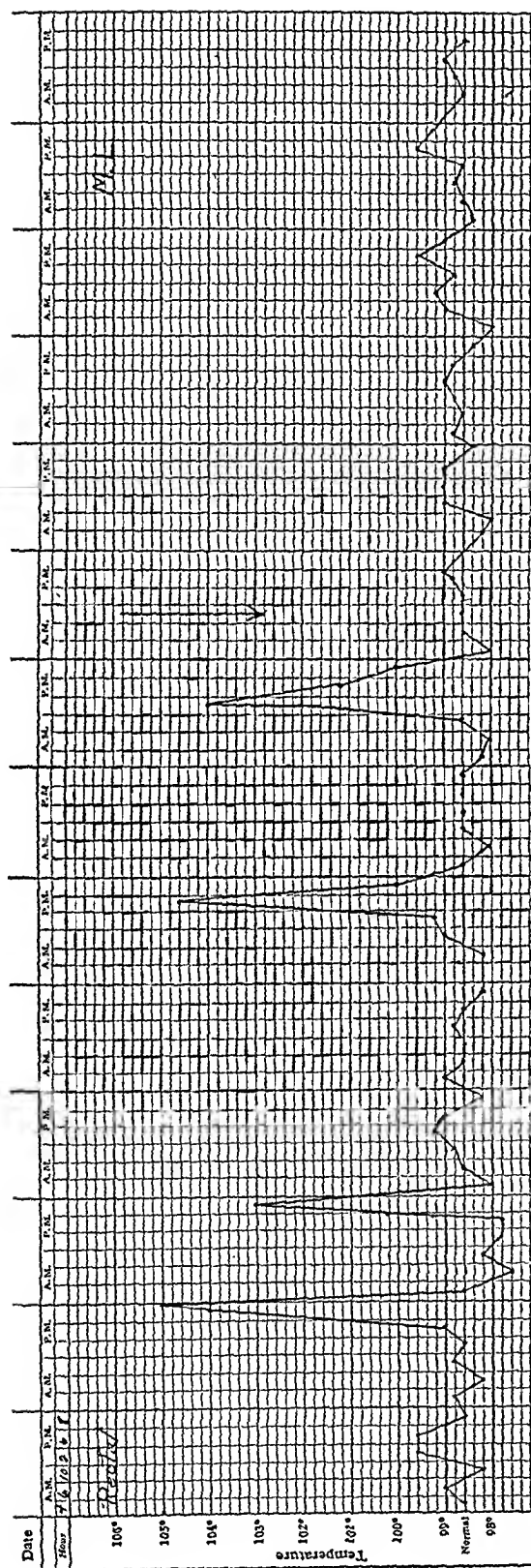


FIG. 7

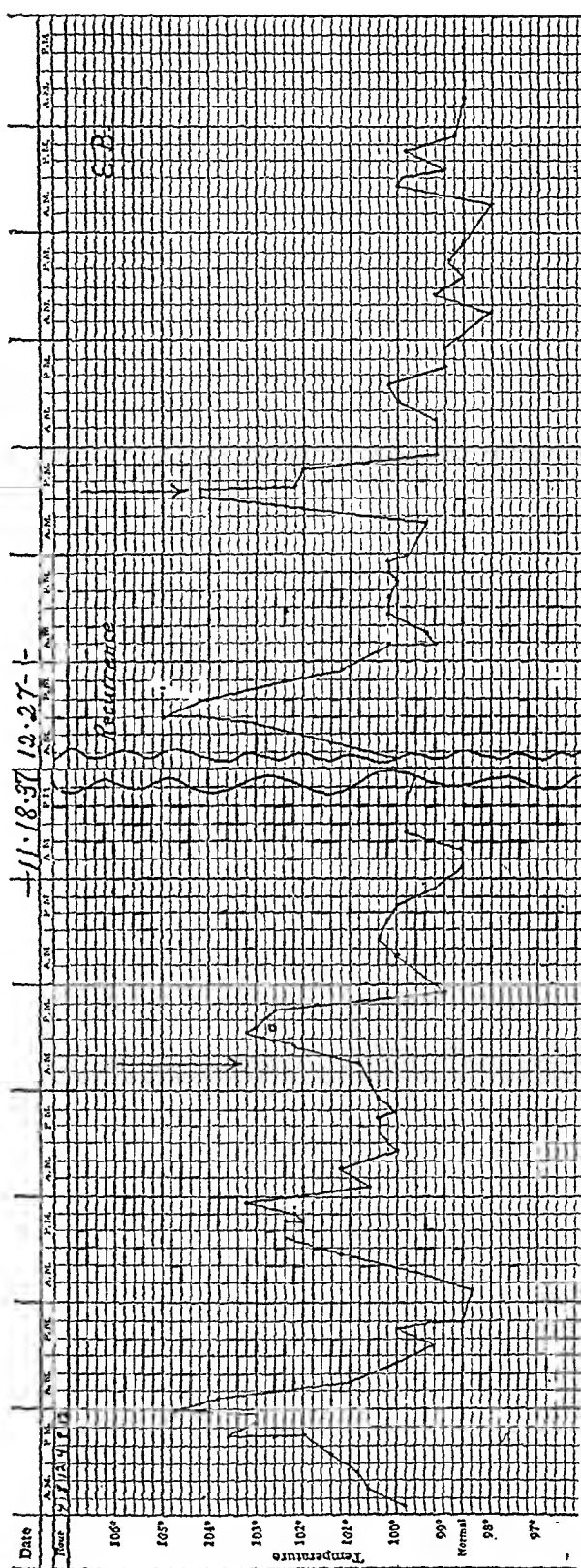


FIG. 8

FIGS. 1 to 7.—The behavior of the malarial fever following termination with mapharsen at the point indicated by the arrows.

TABLE I.—RESULTS OF MAPHARSEN INJECTIONS.

Case.	Patient.	No. of injections.	Immediate result.	Recurrence	Effect of retreatment.
1	O.L.	11	Good		
2	W.R.	11	"		
3	M.L.	1	"		
4	M.D.	11	"		
5	L.G.	11	"		
6	W.L.	1	"		
7	O.W.	11	"		
8	F.P.	1	"		
9	G.M.	11	"		
10	A.M.	11	"		
11	H.T.	1	"		
12	C.B.	11	"		
13	N.P.	1	"		
14	M.I.	1	"		
15	F.T.	1	"		
16	J.H.	11	"		
17	A.G.	1	"		
18	G.T.	1	"		
19	A.K.	1	"	+	Good
20	G.V.	1	"		
21	C.K.	4	"		
22	E.B.	1	"	+	Good
23	F.C.	1	"		
24	J.C.	1	"		

Recurrences after mapharsen are rare and are encountered only in severe cases which in this series were believed to have been allowed to run longer than was advisable. Only 2 instances are on record and 1 of these is illustrated in the accompanying charts.

The disappearance of the parasites is almost immediate. After 24 hours it is only rarely that a disintegrating form can be found in the blood smears. Splenomegaly begins to disappear almost as rapidly. Within a day the spleen is usually appreciably smaller and within 3 or 4 days has receded behind the costal margin.

Examination of the charts reveals that the timing of the injection to a great extent governs the occurrence or nonoccurrence of a chill following treatment. It is seen that if a chill is to be expected in less than 24 hours it usually occurs in spite of the injection, but if the chill is not due for more than 24 hours or if the injection is given at the height of a chill, no subsequent chill will occur. It has been found that the injection of mapharsen even when the temperature is markedly elevated is without danger.

The therapeutic efficacy of mapharsen and its low toxicity make it an ideal remedy for use in malaria, whether of therapeutic or natural origin. Compared with quinine it is immeasurably more effective. It is probably no more effective than atabrine, but the relative ease of its administration, the comfort of the patient in not having to take a somewhat irritant drug and the absence of danger of unpleasant yellow discoloration of the skin or toxic changes in the viscera again make mapharsen the drug of choice.

Unfortunately, no opportunity has been had to test the efficacy of this remedy in estivo-autumnal malaria. It is most important

to determine what effect if any it will have on the notoriously resistant gametocytes of malignant malaria.

The charts will serve as case reports for the therapeutic malaria cases treated with mapharsen. The case of naturally occurring malaria will be recited briefly:

Case Report. C. K., aged 33, white, male, contracted malaria probably late in Aug., 1936, while travelling through Arkansas marshes on an automobile tour. The patient gave a history of a very stormy febrile course prolonged in spite of treatment to 5 weeks. Following this, the patient would have recurrences at intervals of 1 or 2 weeks sometimes in spite of taking 10 or 15 grains of quinine daily. He had been found sensitive to atabrine according to the physician taking care of him at that time. The recurrences usually lasted from 2 to 5 days and were characterized by fever of irregular type from 101 to 103° F., aching bones and severe malaise. The patient was first seen in May, 1937, during one of these recurrences. Parasites were numerous in the peripheral blood. Following injection of 0.05 gm. of mapharsen the symptoms rapidly disappeared. Later the patient was given 3 more injections of mapharsen at weekly intervals with quinine for 3 days of each week for 3 weeks. He had no recurrence following the first injection of mapharsen and has remained symptom free and free of parasites for 8 months.

Conclusions. 1. Mapharsen, a recently introduced arsenated benzene compound for use in syphilis, has been used with strikingly good effect in tertian malaria both of natural origin and artificially inoculated.

2. The effectiveness of this drug and its safety compare favorably with other commonly used malaricidal compounds effective on the asexual stages of the parasites.

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THE USE OF 2 (p-AMINOBENZENESULPHONAMIDO) PYRIDINE IN THE TREATMENT OF PNEUMONIA.

A PRELIMINARY REPORT.

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DURING the past few months there have appeared in the British medical literature encouraging reports on the use of a new sulph-anilamide derivative, M. & B. 693 (2 [p-aminobenzenesulphonamido] pyridine) in the treatment of pneumonia. We have begun to use

this material* in pneumonia patients admitted to several Philadelphia hospitals.

Experimental work, as reported by Whithy,⁹ showed that the action of M. & B. 693 was similar to that of sulphanilamide in hemolytic streptococcus and meningococcus infections in mice. It was found that the drug had a definite action on pneumococcus Types I, VII and VIII, and to a lesser extent on Types II, III and V. Whithy observed that the drug caused degeneration and subsequent disappearance of the capsule of the pneumococcus. M. & B. 693 is reported to possess a low toxicity for animals, does not produce porphyrinuria, and is active in relatively small doses. Wien¹⁰ found the toxicity of M. & B. 693 to be approximately 25% of that of sulphanilamide in mice. Even when administered to dogs and cats in large doses over a considerable period, no untoward reactions were observed. Fleming,⁵ in *in vitro* studies, observed that the drug was antibacterial against both hemolytic streptococcus and pneumococcus; and that growth was retarded in human blood in concentrations which, it is reasonable to suppose, can be obtained therapeutically. In the concentrations which he used, however, it was not bactericidal except in the presence of leukocytes. He found that the action of the drug was greater in immunized blood, which suggested that the best clinical results may be obtained in combination with the use of type-specific sera.

Among the early clinical reports was that of Telling and Oliver,⁸ who reported 2 cases of pneumonia treated successfully with M. & B. 693. The only evidence of toxicity which they observed was a moderate degree of cyanosis in 1 case. Bacteriologic study of their patients confirmed the earlier experimental studies that the drug caused a decapsulation and consequent loss of type specificity of the organism. The largest number of cases and the most complete study has been reported by Evans and Gaisford.⁴ These investigators treated 100 cases of pneumonia with M. & B. 693, and used as a control group 100 cases which received various other forms of therapy. All cases in both groups were unselected, except for 3 that died within 24 hours after admission. The mortality rate in the group treated with M. & B. 693 was 8%, as compared to 27% in the control series. Of the 8 fatalities in the treated group, 6 received less than the minimal adequate dosage. The method of dosage in the majority of cases was the oral administration of an initial dose of 2 gm., followed every 4 hours with 1 gm., until a total of 25 gm. of the drug had been given. As much as 9 gm. was given during the first 24 hours to some of the more severe cases. No constant effect on the hematopoietic system was noted, although in 3 cases that survived the leukocytes fell to 5000. The only other evidence of toxicity was the presence of cyanosis in approximately 25% of the cases treated with large amounts of the

* M. & B. 693, manufactured by the English firm of May & Baker, was supplied to us through the courtesy of Merck & Co.

drug. There was no evidence of renal damage as determined by urine analysis in all treated cases and autopsy in those that died. Christie¹ reported a successfully treated case, and observed no toxic effects other than slight cyanosis. Other workers^{2,3,6,7} have recently published data concerning the use of M. & B. 693 in gonococcus and meningococcus infections and have not mentioned any serious toxic reactions.

During the past few weeks we have had the opportunity of observing the effect of M. & B. 693 in 4 cases of pneumonia, in 1 of which both the drug and type specific serum were used. All 4 recovered. We wish in this brief report to record 2 of the patients treated only with the drug.

Case Reports. CASE 1.—A. J., a 29-year-old white male, was admitted to the medical service of Dr. Samuel Lowenberg at the Philadelphia General Hospital on August 15, 1938. Except for a slight head cold of several weeks' duration the patient had been in good health until 6 days before admission, at which time he complained of general malaise, loss of appetite and chilliness. On the following day there was fever and pain in the right chest, with rusty sputum appearing 2 days later.

Physical examination revealed an acutely ill white man with marked dyspnea, moderate cyanosis and limitation of movement of the right chest. The tongue was heavily coated and over the right upper chest anteriorly was percussion dullness, increased tactile fremitus and vocal resonance, tubular breathing, whispered pectoriloquy and a few fine moist râles. The abdomen was moderately distended. The diagnosis of right upper and right middle lobe pneumonia was made and confirmed by Roentgen ray examination on the same day. The sputum, on typing and culture, revealed a predominance of pneumococci Type I. The blood culture was negative. See Chart I for leukocyte counts, dosage of drug (M. & B. 693), temperature, respiration and pulse readings.

The patient received an initial dose of 2 gm. (M. & B. 693) which was followed by 1 gm. every 4 hours thereafter until 16 gm. had been given. During the next 2 days the patient received 1 gm. every 6 hours for 5 doses, making a total of 25 gm. in all. The only evidence of drug toxicity was an attack of vomiting following the first 12 gm. of the drug. At the time of the fall of temperature, 24 hours after beginning the drug, the patient felt greatly improved and from that time on made an uneventful recovery. The physical findings presented evidence of resolution about the 10th day of the illness and at the time of discharge no signs of lung involvement were detectable. Chest Roentgen ray at that time was also negative. Routine urine studies throughout the illness were essentially negative.

Aside from the usual routine care given pneumonia cases the patient received no therapy other than M. & B. 693.

CASE 2.—C. B., a colored male, aged 24, was well until several days before admission, when he contracted a rather severe head cold. Two days later, August 17, 1938, he experienced a sudden, sharp pain in the left chest, followed the next morning by shortness of breath, cough, rusty sputum and sores on the lips. On August 19 the patient was admitted to Dr. David Riesman's service at the Philadelphia General Hospital.

Physical examination revealed a well-developed male negro in acute respiratory distress, who was coughing up a moderate amount of blood-tinged sputum. There were several herpetic lesions on the lower lip. The left chest presented definite limitation of movement and over the left upper lobe there was dullness to percussion, increased tactile fremitus and vocal resonance, prolonged breath sounds and a friction rub. The diag-

nosis of left upper lobe pneumonia was made. The sputum showed a predominance of Type VIII pneumococci on typing and culture. Blood culture taken the following morning was reported as negative. Repeated urine analyses all negative (see Chart I).

This patient was treated in the same manner as Case 1, except that the drug was discontinued after 21 gm. had been given.

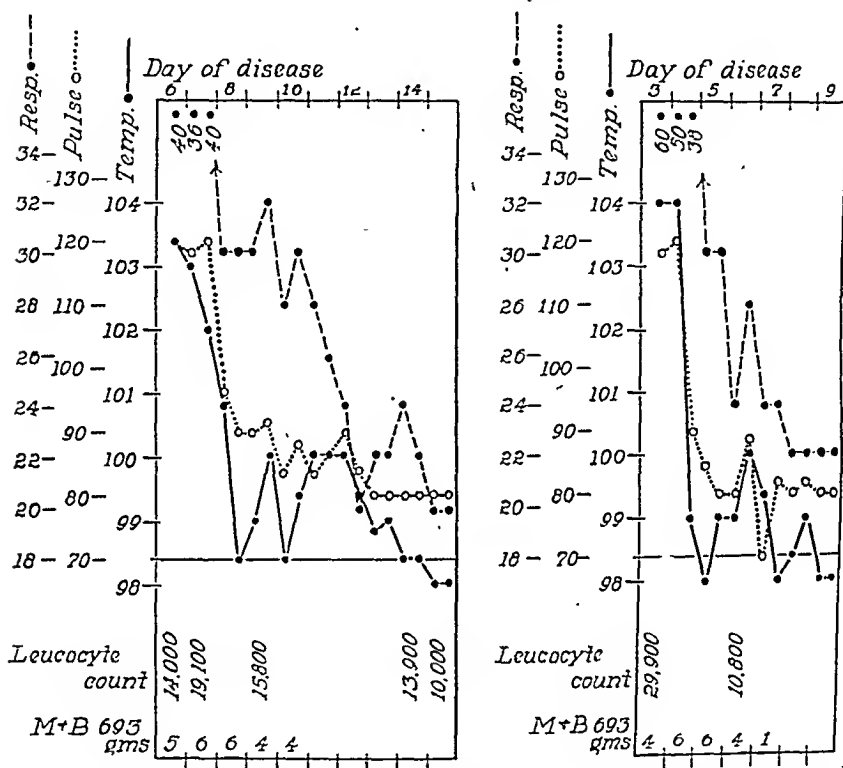


CHART I.—Leucocyte counts, dosage of drug (M. & B. 693), temperature, respiration and pulse readings.

There were no signs of toxicity attributable to the specific medication. Physical examination on the third day revealed bronchial breath sounds as well as many fine moist râles over the left upper lobe. The patient left the hospital on August 25, after an uneventful recovery. At the time of discharge Roentgen ray examination of the chest was negative. No other form of therapy was used except the usual routine measures in such cases.

Discussion. A review of the animal experiments and clinical studies which have been made with M. & B. 693 suggest that this drug has a direct effect upon the pneumococcus, in that it causes capsular degeneration and ultimate decapsulation of the organism with a resultant loss of type specificity. Studies *in vitro* suggest that any bactericidal effect which the drug possesses is dependent upon the presence of leukocytes, and there is some evidence that the drug may be more effective when combined with specific sera. The toxic reactions caused by M. & B. 693 are apparently no more

frequent than those encountered with sulphanilamide, and according to the majority of investigators, are much less severe. Those most commonly noted being moderate cyanosis and occasional vomiting. In Case 1 vomiting occurred following the administration of the first 12 gm. of the drug, but did not reappear even though the medication was continued. In the series of 100 cases reported by Evans and Gaisford,⁴ 3 instances of mild leukopenia were recorded without fatality. There was no evidence in our patients that the drug affected bone-marrow activity. M. & B. 693 is administered orally, and is usually followed in 24 hours by a marked drop in temperature. A slowing of pulse and respiration accompanies this fall in temperature.

From the clinical and experimental studies already reported, and from our limited experience, we believe that the drug should receive a thorough trial in this country. This we plan to do.

Summary. 1. A new chemotherapeutic agent, M. & B. 693, said to be beneficial in the treatment of pneumococcus pneumonia, has recently been reported.

2. Reported experimental and clinical observations suggest that this drug has a definite effect upon the capsule of the pneumococcus.

3. The toxic manifestations of the compound appear to be relatively less than those of sulphanilamide.

4. Our limited experience with M. & B. 693 would suggest that it deserves an extended trial.

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PARTIAL AND COMPLETE HEART BLOCK IN ACUTE CORONARY ARTERY OCCLUSION.

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Introduction. In the present report we submit a detailed analysis of the disturbances in auriculoventricular conduction in 375 cases

of coronary artery occlusion, including a consideration of partial and complete heart block and simple prolongation of the *P-R* interval. In previous papers^{68a,b} a similar analysis has been made of the other arrhythmias.

It has usually been thought that heart block was very rare.^{4,90,99} Close scrutiny of the literature, however, has revealed a considerable number of cases, which leads to the conclusion that the association of heart block and coronary occlusion is not so infrequent as was thought.

In 1876, in the first diagnosis of coronary thrombosis suggested at the bedside and confirmed at necropsy, Hammer¹¹ was struck by the very slow heart rate of the patient, only 8 beats per minute. The significance of this escaped him but it is almost certain that complete heart block existed. Ten years later Huchard¹² recorded a case of Stokes-Adams syndrome associated with "angina pectoris." Other early reports of heart block and coronary artery occlusion were made by Jellieck, *et al.*¹³ and Gallavardin and Dufour.³⁰ In 1913 and 1914 Oppenheimer and his colleagues^{71,75} made the first careful anatomic studies of the hearts in 4 cases of Stokes-Adams syndrome and found that in 2 of them the syndrome was the result of occlusion of one or more coronary arteries.

The first clinically recognized cases of coronary artery thrombosis associated with complete heart block and the Stokes-Adams syndrome were described by Levine and Tranter⁶² in 1918 and Gallavardin²⁹ in 1922. Since then numerous reports of single instances of heart block in coronary thrombosis have appeared in the literature^{1,3,9,10,12,14,15,20,25-29,32,39,42-44,52,57,59,65,71,72,78,82-84,86,89,93,94} comprising more than 35 cases described in detail. Kerr⁵⁵ collected 5 cases.

Recently Schwartz⁶⁷ presented 15 cases of *A-V* dissociation and Stokes-Adams syndrome in coronary artery occlusion which he had personally observed. Such an experience is unique, for no other author has reported such a large series. An analysis of approximately 1500 unselected cases of coronary artery occlusion included in 17 fairly large series reported during the last 15 years,^{2,21-24,46,47,50,61,77,79,81,85,91,93,96,98} reveals that the incidence of complete heart block varied from 0.7 to 10%. The highest incidence, 10%, is probably not typical since it was derived from two small series, 19 and 30 cases respectively, and included only fatal cases examined post-mortem. Omitting these two small series, the incidence varied from 0.7 to 4%, the average being 1.5%; the number of cases of complete heart block totalled 21. Less attention has been paid to partial heart block, including *P-R* prolongation and dropped beats, probably because the clinical course is less spectacular than that of complete block. There have been only occasional case reports of partial block,^{3,11,13,43,55,73,93} but the incidence in the above quoted series was 2.5%.

Numerous attempts have been made to produce heart block experimentally by ligating the arteries to the conduction system but the results have been conflicting. When the septal artery alone was ligated in the dog, infarction of the septum occurred without heart block.^{8,21,45,53,76} On the other hand, "mass ligation," to include the anastomotic vessels, uniformly resulted in all grades of heart block.^{55,60,101} Similar results were obtained by experimental coronary embolism with lycopodium.^{21,40} In monkeys, in which the vascularization of the septum is similar to that of man, DeWart and his associates⁹⁵ produced heart block by ligation of the right coronary artery which gives off the septal artery, but not by ligation of the left coronary artery.

*Prolonged P-R Interval.** Simple prolongation of the *P-R* interval to 0.20 of a second or longer was observed in 60 (one-sixth) of the 375 patients with coronary artery occlusion who were studied (Table 1). The ratio of males to females in this group was 4:1,

TABLE 1.—A-V HEART BLOCK IN 375 CASES OF CORONARY ARTERY OCCLUSION.

	Prolonged <i>P-R</i> .	Partial heart block.	Complete heart block.	Normal <i>P-R</i> , no arrhythmia.
Number	60 (16%)	6	6	263
Average age (years)	55.5	62	59	56
Sex—Male:Female	4:1	1:1	1:5	4:1
Mortality	15%	2 (33%)	4 (67%)	24%
Attack—1st	57%	5 (83%)	2 (33%)	52%
Multiple	43%	1 (17%)	4 (67%)	48%
Hypertension	66%	3 (50%)	6 (100%)	65%
Enlarged heart	63%	3 (50%)	5 (84%)	60%
Heart failure	66%	5 (84%)	6 (100%)	72%

identical with that in the general series. Similarly, the average age and the incidence of previous attacks, hypertension, cardiac enlargement and heart failure were practically the same as in the patients without *P-R* prolongation. The mortality rate in the patients with *P-R* prolongation, 15%, was actually lower than in the entire series, 24%. It appears therefore that the presence of simple *P-R* prolongation exerted no adverse effect on the clinical course or prognosis.

This conclusion is valid even if 23 cases with a *P-R* interval of only 0.20 second, usually considered the upper limit of normal, are excluded. However, 0.20 second was probably significant in most of these cases, for the *P-R* interval became shorter at some time in the course of the study. In 31 patients (more than one-half), the *P-R* interval was prolonged to 0.22 second; in 3 to 0.26 second; in 2 to 0.30 to 0.34 second and in 1 to 0.40 second. There were no dropped beats in the latter cases despite the excessive prolongation in *A-V* conduction time.

In three-fifths of the cases the *A-V* conduction disturbance appeared during the first week after the attack (Table 2). In nearly one-third a prolonged *P-R* interval was noted on the first or second day. In almost one-fifth, however, the *P-R* interval did not become prolonged until the third, fourth or even sixth week (Fig. 1). Occasionally a prolonged *P-R* interval, which had become normal early in the attack, reappeared several weeks later without any other change in the clinical condition or in the electrocardiogram of the patient (Fig. 2).

The duration of the *P-R* interval prolongation was more than 1 week in 77% of the 43 cases in which it could be determined (Table 2). It was from 1 to 3 weeks in 6 patients, 1 to 2 months in 11,

* The average number of electrocardiograms taken on each patient was 8. The chest lead shown in the illustrations was taken with the left leg electrode in the left midclavicular line, and the right arm electrode on the left leg, in conformity with the method officially accepted by the American Heart Association (Am. Heart J., 15, 107, 1938).

3 to 6 months in 9 and was still present after 1 to 2 years in the remaining 7. It appears, then, that *P-R* prolongation may become permanent (Fig. 3), thus differing from other arrhythmias in coronary artery thrombosis which are usually transient.^{68a,b}

TABLE 2.—TIME OF ONSET AND DURATION OF HEART BLOCK.

Time of onset:	Prolonged <i>P-R</i> .	Partial heart block.	Complete heart block.
1-2 days	19	4	4
3-7 days	18	2	1
2-3 weeks	15	0	0
4-6 weeks	7	0	0
Unknown	0	0	1
Duration:			
1-4 days	6	2	3
5-7 days	6	3	0
2-3 weeks	6	0	2
1-2 months	11	0	1
3-6 months	9	0	0
1-2 years	7	1	0

When prolongation of the *P-R* interval persists following coronary artery occlusion, a subsequent attack will often produce a further increase in the conduction disturbance. An instructive illustration of this point is a 50-year-old man whom we observed in three attacks. In the first attack the *P-R* interval measured 0.19 second. After the second it was prolonged to 0.22 second and following the third it increased further to 0.28 second.

Simple *P-R* prolongation was associated with an arrhythmia in only a few patients; 2 developed paroxysmal auricular fibrillation and 1 both paroxysmal auricular tachycardia and ventricular bigeminal rhythm. On the other hand, 16 patients with *P-R* prolongation (26.5%) also had bundle-branch or intraventricular block, an incidence twice as great as in patients with a normal *P-R* interval. Impaired intraventricular conduction was especially common when the *P-R* interval measured more than 0.24 second, being present in 3 of the 6 patients (Fig. 4). This association is emphasized by the case described above, in which both the *P-R* and the *QRS* interval increased progressively after each of three attacks.

An attempt was made to correlate the presence of *P-R* prolongation with the site of infarction (Table 3). In 23 patients it was associated with a *Q-1 T-1* pattern in the electrocardiogram, typical of anterior wall infarction, and in 17 with a *Q-3 T-3* pattern seen in posterior wall infarction. In 10 cases there were signs of both anterior and posterior infarction and in the remaining 10 the changes in the electrocardiogram were atypical. Although, electrocardiographically, anterior infarction seems to be somewhat more frequent than posterior, the small difference does not permit of a definite conclusion. Postmortem examination in 5 of the 8 fatal cases also revealed no specific lesion as a cause for the *P-R* prolongation, both coronary arteries being occluded with equal frequency.

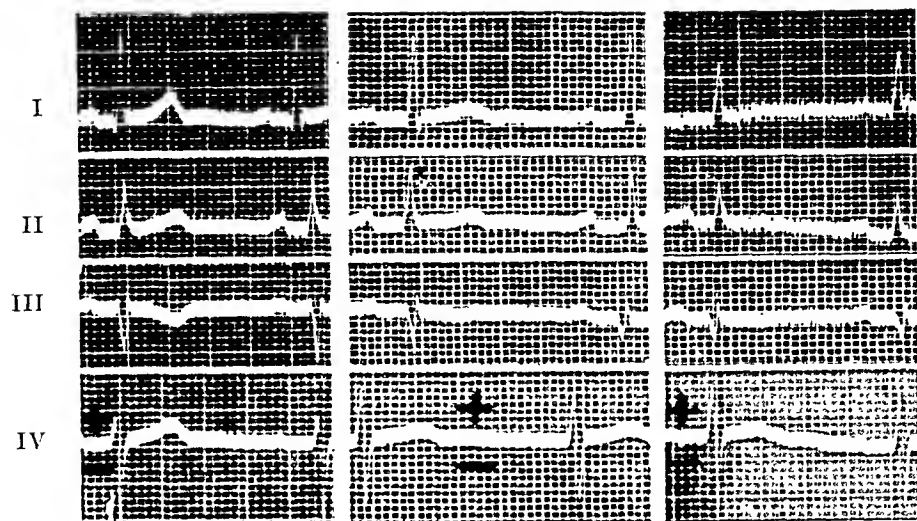


FIG. 1

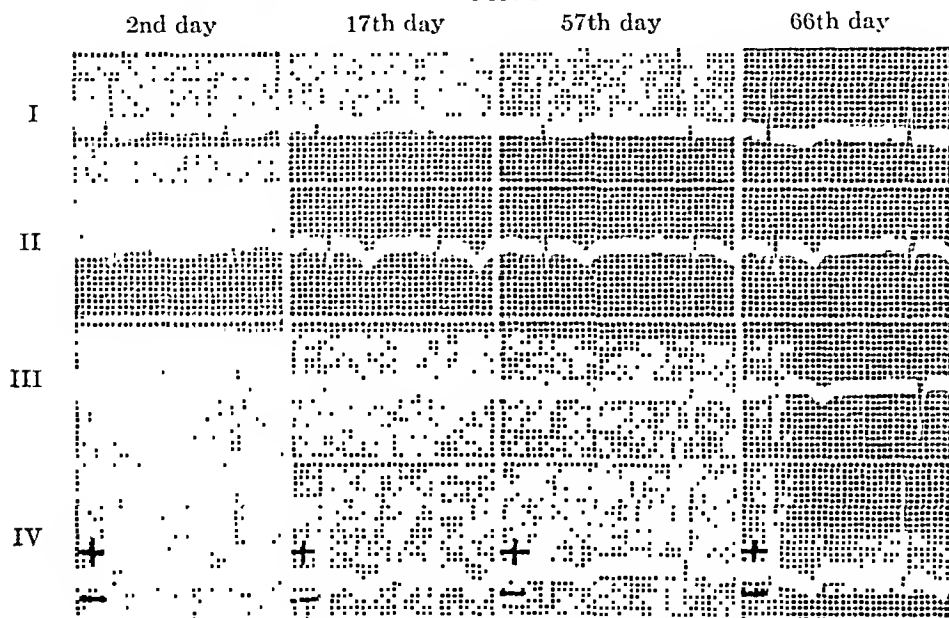


FIG. 2

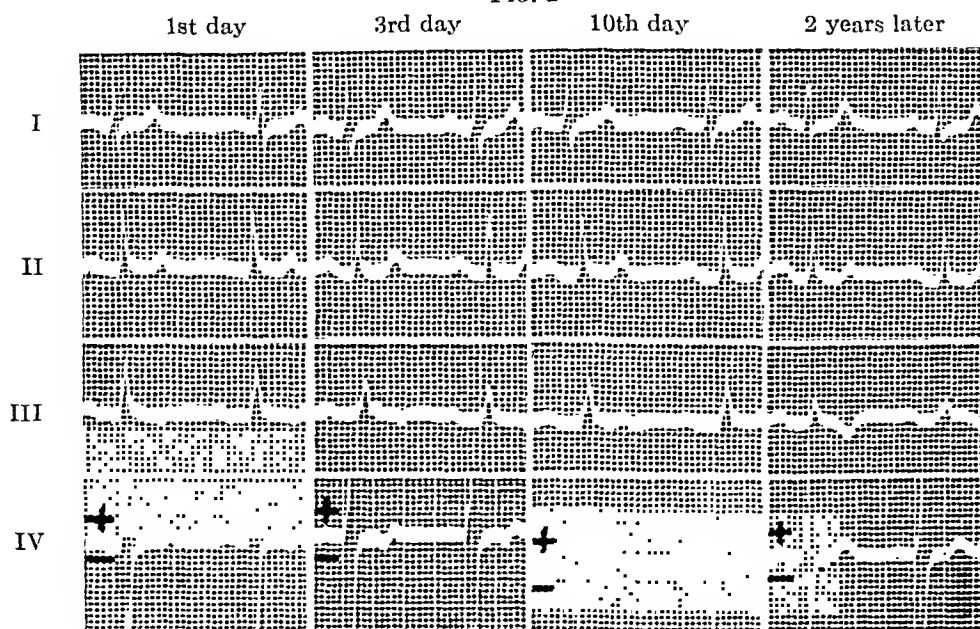


FIG. 3

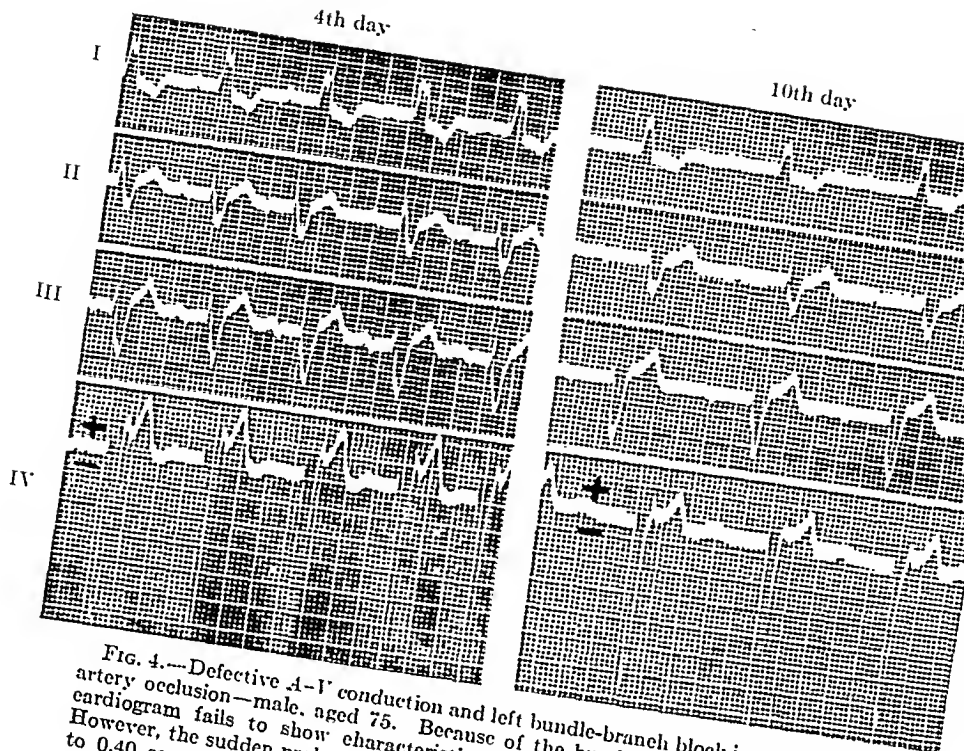


FIG. 4.—Defective A-V conduction and left bundle-branch block in acute coronary artery occlusion—male, aged 75. Because of the bundle-branch block the electrocardiogram fails to show characteristic progressive changes of acute infarction. However, the sudden prolongation of the *P-R* interval from 0.26 sec. on the 4th day to 0.40 sec. on the 10th day is diagnostic of acute damage. Necropsy revealed recent and old occlusions of the right coronary artery with infarction and aneurysmal dilatation of posterior wall of left ventricle and septum.

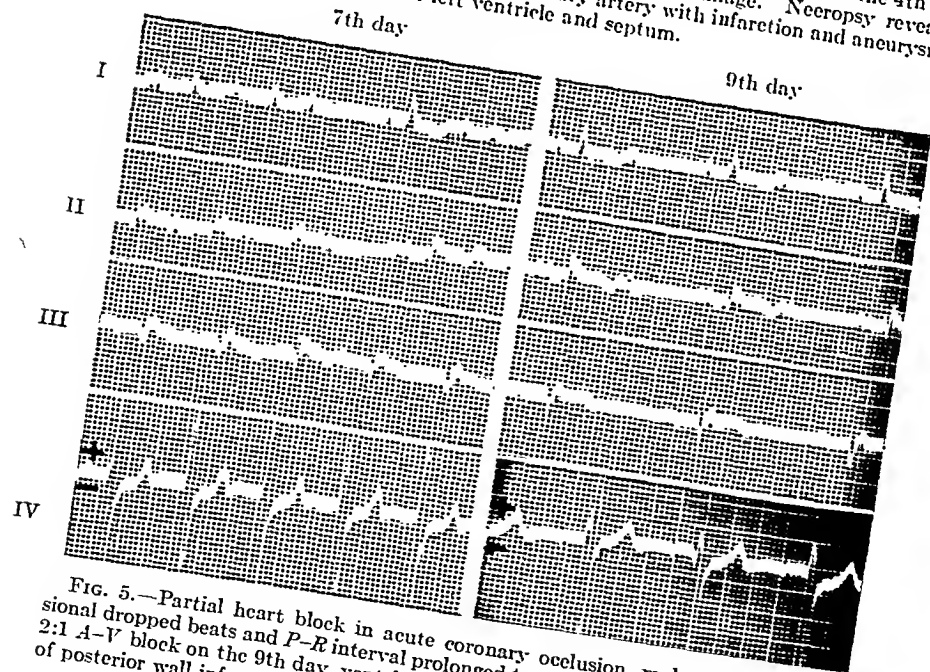


FIG. 5.—Partial heart block in acute coronary occlusion, male, aged 66. Occasional dropped beats and *P-R* interval prolonged to 0.32 sec. on the 7th day. Occasional 2:1 A-V block on the 9th day, ventricular rate 50. Electrocardiogram characteristic of posterior wall infarction. Death on 10th day.

I

III

IV

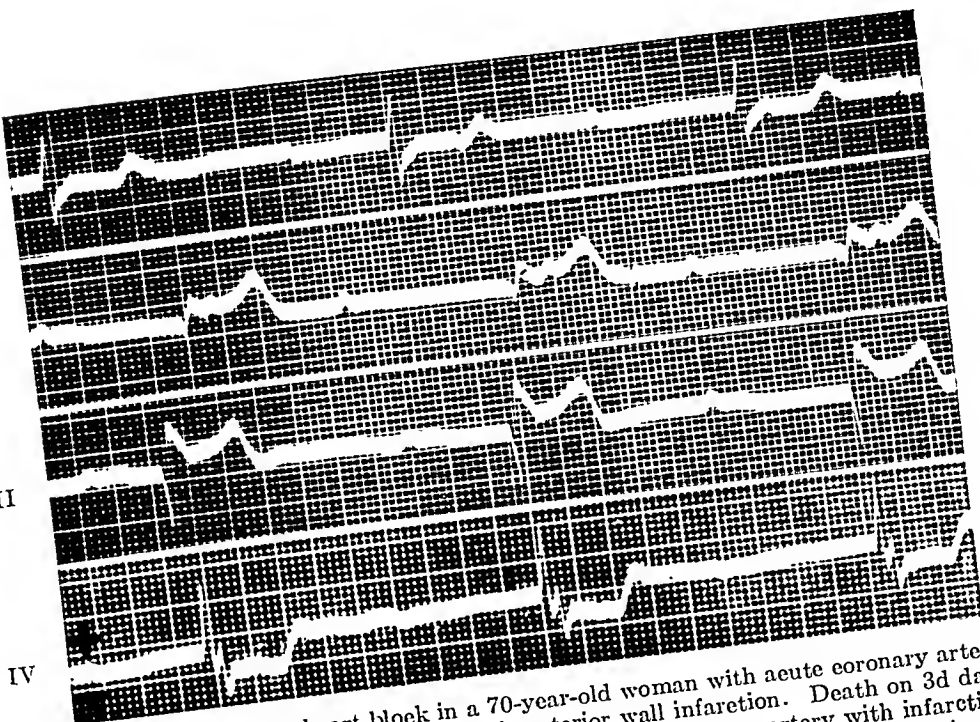


FIG. 6.—Complete heart block in a 70-year-old woman with acute coronary artery occlusion. Typical Q-3 T-3 pattern of posterior wall infarction. Death on 3d day. Necropsy showed recent and old occlusions of right coronary artery with infarction of posterior wall of left and right ventricles and posterior portion of interventricular septum.

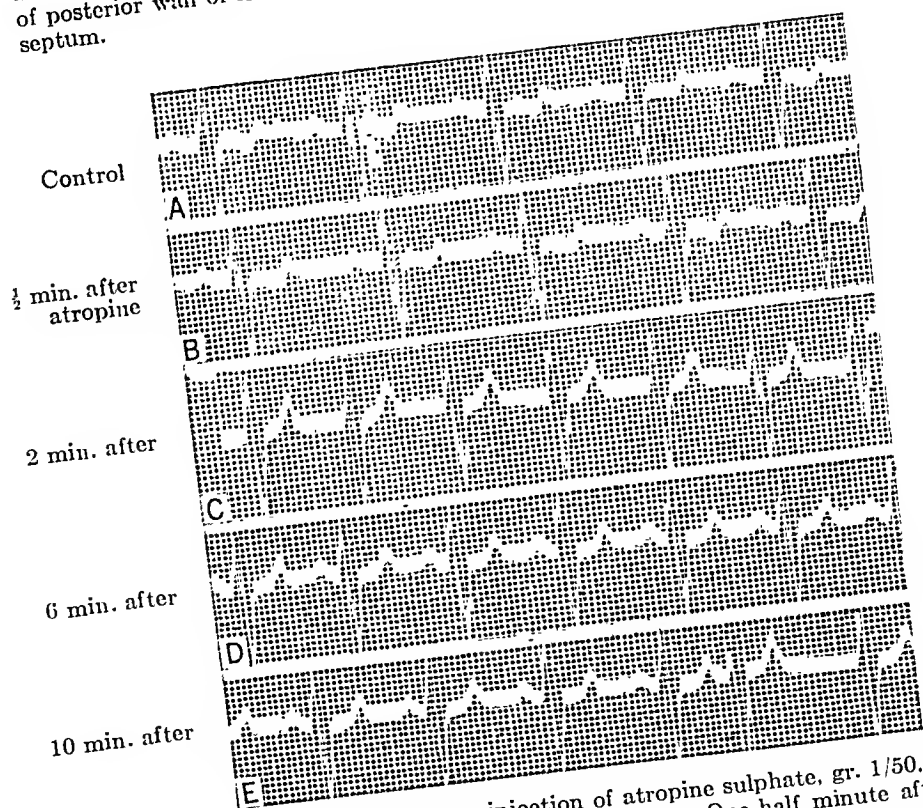


FIG. 7.—Effect of intravenous injection of atropine sulphate, gr. 1/50, on the prolonged P-R interval in acute coronary occlusion. One-half minute after injection the P-R interval has decreased from 0.22 to 0.18 sec. Two minutes later, nodal rhythm, rate 90, appears and persists for several minutes. Six to 10 minutes after injection the P-R interval is still normal, 0.16 sec. The intraventricular conduction defect (QRS 0.15 sec.) is unaffected. This experiment suggests that vagal influences may be responsible in part for prolongation of the A-V conduction time in coronary occlusion.

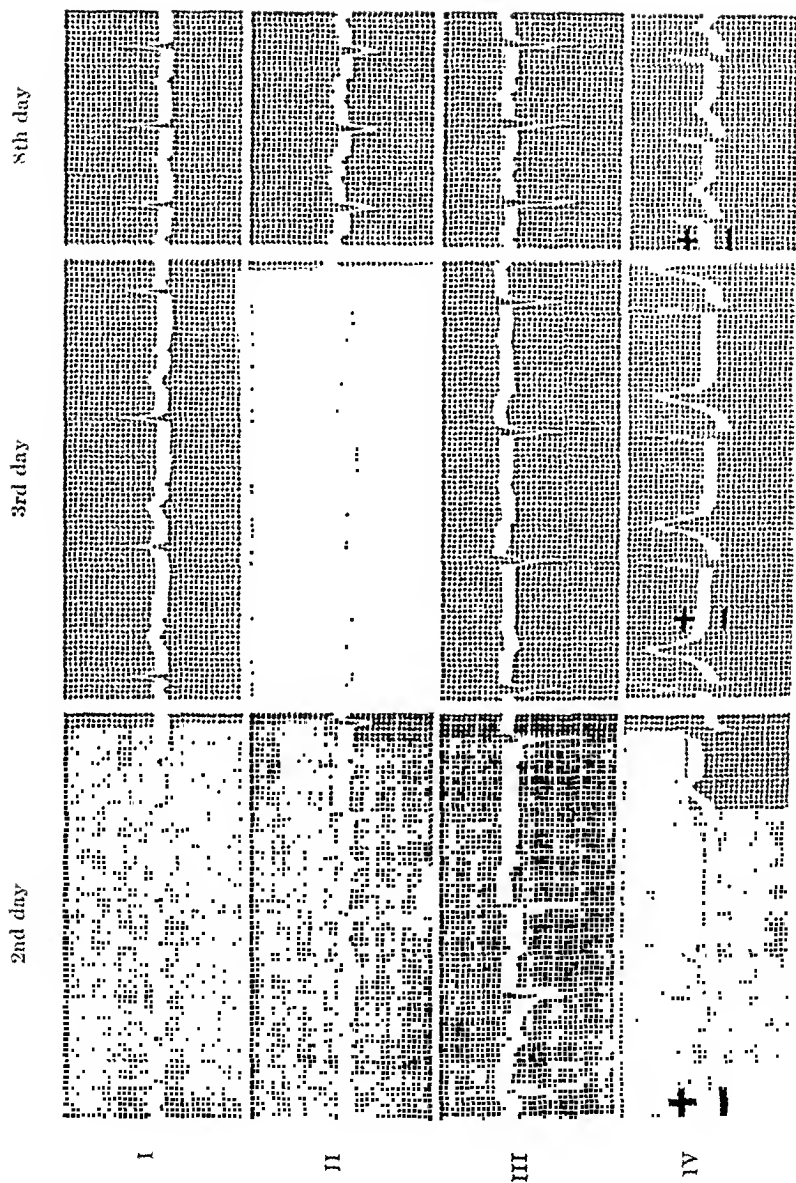


FIG. 8.—Partial and complete heart block in acute coronary occlusion. Male, aged 60. Partial heart block with frequent dropped beats on the 2d day; complete block with ventricular rate of 65 on the 3d day. This persisted until the 8th day, when sinus rhythm, rate 100, returned with a prolonged *P-R* interval of 0.26 sec. Typical *Q-TS*. *T-2*, *T-3* pattern of posterior wall infarction. Necropsy showed recent and old occlusions of right coronary artery with massive infarction of posterior wall of left ventricle and septum.

TABLE 3.—VENTRICULAR RATE. ECG. PATTERN AND ARTERY OCCLUDED.

	Prolonged <i>P-R</i> .	Partial heart block.	Complete heart block.
Average ventricle rate:			
20-40		0	3 (deaths)
40-48		2 (deaths)	0
50-60		2	1
75-100		2	2 (1 death)
ECG. pattern:			
<i>T</i> -1 type	23	1	0
<i>T</i> -3 type	17	5	6
<i>T</i> -1-2-3 type	10	0	0
Atypical	10	0	0
Coronary artery occluded:			
L. A. D.	2	0	0
Right	2	1	4
Left and right	2	0	0

A-V Heart Block. Auriculoventricular block other than simple *P-R* prolongation was present in 12 (3.2%) of the 375 patients (Table 1); partial block with frequent dropped beats in 6 (Fig. 5); complete *A-V* dissociation in 3 (Fig. 6) and both types in the remaining 3 (Fig. 8). Unlike the finding in coronary thrombosis in general, women in this group outnumbered men 2:1. The average age also was higher, 60.5 years as against 56 years in the entire series.

The patients in this group ran a severe clinical course and presented evidence of severe myocardial disease. Heart failure, usually both left and right, was practically universal. Four of the 6 patients with complete block and 1 with partial block had sustained a coronary occlusion in the past (Table 1). Previous hypertension and cardiac enlargement were present in all except 1 case of complete heart block but in only half of those with partial block. Six of the patients died, a mortality rate of 50%. These included 4 patients with complete *A-V* dissociation and 2 with partial heart block.

In 8 of the 12 patients, including 4 with complete block, the block set in on the day of the attack (Table 2); in 2 it began on the third day, in 1 on the fifth and in the remaining case the day of onset could not be determined. Heart block thus occurs very early in coronary occlusion.

The duration of the heart block was variable (Table 2). With partial block, the duration was 2 days in 1 case and less than 1 week in 3; in another case, 2:1 *A-V* block persisted until death 1 year later. In the group with complete heart block, 3 patients died within 2 days following the onset of the attack, the heart block remaining unchanged. In the fourth patient, conduction through the *A-V* system gradually improved so that sinus rhythm with a prolonged *P-R* interval returned on the tenth day (Fig. 8). In spite of this the patient died the following day with increasing heart failure, presumably as a result of very extensive infarction. In the

fifth patient the block lasted at least 2 weeks and in the sixth was intermittent, periods of partial and complete block alternating with periods of normal rhythm for more than a month.

The electrocardiographic findings (Table 3) were of great interest for, with one exception, all the cases of partial or complete block presented the *Q-3 T-3* pattern characteristic of infarction of the posterior surface of the heart following occlusion of the right or left circumflex coronary artery (Figs. 6, 8). The lone exception, a patient with 2:1 heart block, presented the *T-1* type of electrocardiogram usually seen in occlusion of the left anterior descending artery. Although the patient died of heart failure 1 year later, permission for necropsy was not obtained and we were unable to determine whether there was occlusion of the right coronary artery as well as of the left anterior descending artery.

The postmortem studies corroborated the electrocardiographic findings (Table 3). The 4 fatal cases of complete block and 1 of the 2 fatal cases of partial block were examined; in each there was extensive infarction of the posterior portion of the interventricular septum and posterior surfaces of both ventricles, resulting from occlusion of the right coronary artery. In 2 of these cases the left circumflex artery was also occluded. Only 1 case showed acute occlusion of the left anterior descending artery in addition to the right coronary artery. However, all showed one or more old occlusions of all 3 arteries. It is therefore not surprising that the acute infarction in all the cases was massive and that advanced heart failure existed.

Three of the 5 cases with complete *A-V* dissociation and 1 of those with partial block were further complicated by abnormally wide *QRS* complexes (0.12 to 0.13 second), resulting from an abnormal ventricular focus or impaired intraventricular conduction (Fig. 6). Infarction of the interventricular septum, present at autopsy in all the cases examined, might not only impair conduction through the *A-V* node and main stem of the bundle of His in the upper part of the septum, but might also interfere with conduction through the bundle-branch system in its lower part. The remaining 5 patients with partial block all had *QRS* complexes of normal appearance and duration. It may be that the septal infarction in these cases was not extensive.

Clinical Features. Disturbances in auriculoventricular conduction give rise to symptoms principally when the block is complete and occasionally in partial block with frequent dropped beats. When the blood supply to the *A-V* node or bundle is occluded and auriculoventricular dissociation occurs, there may be sudden cessation of ventricular contraction for a brief period. As a result of the ensuing cerebral anoxemia, the patient may develop syncope or convulsions, *i. e.*, the Stokes-Adams seizure. As the ventricle assumes its own rhythmic contractions and the cerebral flow be-

comes adequate, these symptoms disappear. However, the ventricular rate in complete block is usually between 20 to 40, which is too slow to maintain sufficient blood supply to the brain when associated with the low blood pressure and diminished cardiac output present in coronary artery occlusion. Therefore, when a ventricular rate of 40 or less persists, repeated attacks of syncope or convulsions are apt to occur and the patient not infrequently lapses into unconsciousness or coma. In our cases with complete block the latter type of Stokes-Adams syndrome was the commonest, appearing in all 3 of the 5 cases in which the ventricular rate was 20 to 40 beats per minute. In another patient, periods of complete *A-V* dissociation alternated with intervals of 2:1 block and normal sinus rhythm. During the intervals of block the ventricular rate fell as low as 45 beats per minute and the patient experienced mild syncopal attacks; when the rate rose, these did not occur. In the remaining 2 patients the ventricular rate remained above 75 beats per minute and the block caused no symptoms. In the 6 cases with partial heart block the ventricular rate did not fall below 40; in 2 cases it varied between 75 and 100. Only 1 of these patients presented cerebral symptoms; this was a 70-year-old woman with a 2:1 heart block and a ventricular rate of 50, who was admitted to the hospital in coma, which was attributable not to the slow rate alone but also to the severe degree of shock and congestive heart failure present. It is noteworthy that even this patient survived, although the 3 patients with complete heart block and a rate of 40 or less ended fatally. When *P-R* prolongation was present the heart rate was always above 60 and no cerebral symptoms occurred.

The slow ventricular rate in heart block not only manifests itself by Stokes-Adams seizures but also leads as a rule to severe congestive failure. This is further evidence of the inability of the badly damaged heart to maintain a normal rate of blood flow in the presence of a slow heart rate and low blood pressure.

Except for these manifestations of a slow ventricular rate, *A-V* conduction disturbances give rise to few physical signs other than those usually associated with coronary artery occlusion. When complete *A-V* dissociation is present, the auricular sounds may be distinct, and occasionally the auricular wave is visible in the cervical veins. Partial block with dropped beats produces an irregularity of pulse which may be difficult to differentiate from other arrhythmias such as premature beats or even auricular fibrillation. The diagnosis usually depends on the electrocardiogram and this is also the only means of detecting *P-R* prolongation, since the heart rate is regular and not slow, and there are no signs or symptoms attributable to the mild conduction disturbance.

Syncope and coma produced by heart block in coronary artery occlusion must be differentiated from these conditions as produced by other causes, such as severe shock and cerebral vascular acci-

dents, particularly embolism. We have already pointed out that in coronary artery occlusion with shock, there is a diminution in cardiac output and a marked drop in blood pressure which may result in cerebral anemia, and consequently, syncope or coma, even with a normal heart rate. It is noteworthy that these conditions obtain early in the attack when heart block also is apt to occur, and when syncope is present both causes should be considered.⁶¹ Clinical observation of the pulse will usually determine the diagnosis; if it is slow, *i. e.*, 40 beats per minute or less, complete heart block is probably present. It must be remembered, however, that cerebral disturbances alone may also result in reflex slowing of the heart rate; therefore it may be necessary to rule out heart block by the electrocardiogram. Embolism to the brain from intramural thrombosis may give rise to cerebral symptoms identical to those of heart block but this usually occurs later in the course of the attack and the heart rate is not slowed.

The sudden appearance of auriculoventricular block may be, as in other arrhythmias, the first, and occasionally the only, indication of occlusion of a coronary artery, as Levine and Tranter⁶² emphasized. It is important to consider the possibility of coronary occlusion in the presence of a sudden onset of heart block. This is particularly true when the block is accompanied by the Stokes-Adams syndrome which may completely mask the other features of the occlusion, such as pain.

Simple prolongation of the *P-R* interval may be of great diagnostic significance since it is occasionally the only electrocardiographic abnormality (Fig. 1). A case in point is that of a 50-year-old man who was admitted to the hospital following a prolonged attack of precordial pain. Although typical clinical signs of coronary artery occlusion were present, including a drop in blood pressure, fever and leukocytosis, repeated electrocardiograms failed to show any change until 3 weeks after the attack, when the *P-R* interval became lengthened to 0.24 second. This case also illustrates the necessity of taking records persistently in coronary artery occlusion, for not only may a prolongation of the *P-R* interval be the only change in

LEGENDS FOR FIGS. 1, 2 AND 3.

FIG. 1.—Acute coronary occlusion with normal electrocardiogram except for prolongation of the *P-R* interval. On the 1st day the *P-R* is 0.20 sec. It suddenly becomes prolonged to 0.24 sec. on the 20th day. On the 29th day it is again 0.20 sec.

FIG. 2.—Prolonged *P-R* interval following acute coronary occlusion in a 60-year-old woman. *Q-3 T-3* type of electrocardiogram. The *P-R* interval is prolonged to 0.22 sec. on the 2d day; normal on the 17th day (0.14 sec.); prolonged temporarily on the 51st day (0.22 sec.), without any other clinical or electrocardiographic change.

FIG. 3.—Permanently prolonged *P-R* interval in a 50-year-old woman with acute coronary occlusion. Progressive prolongation of the *P-R* interval from 0.22 sec. on the 1st day to 0.24 sec. on the 3d day, and to 0.26 sec. on the 10th day. The *P-R* prolongation became permanent, being present after 2 years.

the electrocardiogram, but it may not appear for some time after the attack. Furthermore, when *P-R* prolongation is associated with *T*-wave abnormalities these may remain fixed and the *P-R* interval alone show changes in serial records.

It is interesting to speculate on the relation of coronary artery occlusion to chronic complete heart block or prolonged *P-R* interval. It is probable that in many instances these have been initiated by an occlusion. We have seen that prolongation of the *P-R* interval may persist for months or years after an occlusion and White and his coworkers^{55,81} found that 10 to 12% of 190 cases of chronic heart block had followed a coronary occlusion. Furthermore, anatomic studies in some cases of chronic complete heart block have shown complete occlusion of the arteries supplying the interventricular septum. Postmortem studies have taught us that coronary occlusion is more frequent than has been suspected since it may occur without producing any characteristic history or clinical evidence of the disease.

Smith⁹⁰ stated that coronary artery occlusion rarely occurs in the presence of complete *A-V* dissociation. He cited one exception and Lyon⁶⁶ has observed another. Also 1 of our patients gave a history of syncope before the attack, suggesting the existence of complete heart block.

Pathogenesis. Our cases of complete and partial heart block, as well as the majority of those cited by others, exhibited at necropsy occlusion of the right coronary artery with infarction of the posterior surface of both ventricles and the posterior portion of the interventricular septum. Occasionally only the left circumflex coronary artery has been found occluded, but this too resulted in posterior wall infarction. That the latter was present in the cases not examined pathologically was evidenced by the presence of the characteristic *Q-3 T-3* pattern in the electrocardiogram. These findings can be readily explained anatomically, since auriculoventricular block results from disturbed conduction through the *A-V* node or bundle of His, which are situated in the upper posterior part of the interventricular septum. In 92% of hearts the blood supply to this region is derived from the right coronary artery through the ramus septi fibrosi, the specific artery to the *A-V* node.^{37,67} Sudden occlusion of the right coronary artery above the origin of this branch, or of the specific artery itself, may result in infarction of the upper posterior part of the septum and lead to delay or complete interruption in the passage of the impulse from auricles to ventricles.

One might therefore anticipate some degree of block in all or in the majority of cases in which the right coronary artery is occluded, and since right coronary artery occlusion is as frequent as that of the left coronary artery,^{6,68d,87} heart block should be a common finding. Yet we have seen that it occurs in not more than 5% of cases. There are several reasons for this discrepancy, the most important being

the presence of profuse anastomotic channels between the left and right coronary arteries in the region of the *A-V* node and bundle of His in the upper part of the septum, particularly the arteria anastomotica auricularis magna.^{17,37,38,51,58} Stenosis of the specific artery to the *A-V* node has been observed^{17,51} without clinical or electrocardiographic evidence of any lesion. The collateral circulation is important not only in preventing the onset of heart block, but also in effecting its remission once it has set in. Another explanation of the fact that heart block is not more common in coronary thrombosis lies in the high origin of the ramus septi fibrosi. It has been emphasized by Smith,⁹⁰ Ball⁴ and Wilson¹⁰⁰ that this vessel leaves the right coronary artery proximal to the usual site of thrombosis, so that the circulation to the junctional tissues is rarely compromised.

Although heart block is associated as a rule with occlusion of the right coronary artery, occasionally it follows closure of the left, as illustrated by an electrocardiogram of the *T-1* type in one of our cases, and in one published case.³⁹ Furthermore, postmortem examination in several cases^{3,15,74,88,99,100} revealed thrombosis of the left anterior descending artery with infarction of the upper part of the interventricular septum. That occasional cases of this kind occur is not surprising since we have seen that in 8% of cases the *A-V* node is supplied by the left coronary artery. Furthermore, if there is preëxisting stenosis of the right coronary artery, sudden occlusion of the left may result in heart block because the collateral circulation to the posterior septum has been cut off.

Rarely heart block has been described in the presence of an intact *A-V* node and bundle.^{31,33,75} This was attributed to anoxemia resulting from diminished blood flow. The *A-V* node has been found markedly sensitive to anoxemia.^{18,19,80} Since shock and heart failure are severest within the first few days following the occlusion, anoxemia of the myocardium is greatest during this time and this predisposes to the early appearance of heart block observed in most cases.

The mechanism of the production of heart block thus far discussed is the one generally accepted, but other explanations have been offered. The chief of these is that the block in conduction does not occur in the *A-V* node or main stem of the bundle of His but in the lower part of the interventricular septum where the infarction compromises conduction through both bundle-branches. Several authors^{15,39,67,102} have observed cases of coronary thrombosis in which evidence of bundle-branch block recorded in the electrocardiogram preceded the appearance of heart block. It was thought that the infarction in the septum at first involved one bundle-branch causing bundle-branch block and then the other, producing complete *A-V* heart block.

Although Ball⁴ stated that in complete block the *QRS* complex was

always supraventricular in type, in 3 of our 6 cases with this arrhythmia it measured 0.12 to 0.13 second. Similarly 13 of the 15 cases reported by Schwartz⁸⁷ presented intraventricular block. This suggests that there was simultaneous block in conduction through the bundle of His and one or both of its branches. It is interesting to repeat that the septum in our 3 cases showed very extensive infarction, both in its upper and lower portions.

Unlike the severer grades of block, the electrocardiographic and pathologic changes in *P-R* prolongation were not uniform. The septum was involved in only 3 of the 5 cases. It is probable, therefore, that other factors, in addition to the injury to the *A-V* node, come into play in the production of *P-R* prolongation. The most important of these is doubtless anoxemia to which the *A-V* node and junctional tissues are highly sensitive.^{19,80} Asphyxiation in cats is followed by increasing *A-V* block;⁶³ in dogs and men anoxemia causes a progressive delay in auriculoventricular conduction ending in complete block.³⁶ Clinically, it is known that heart block may occasionally appear during heart failure and disappear after treatment.⁵ Because of the coronary insufficiency and heart failure present in our patients, it is not surprising that so many of them showed a mild decrease in *A-V* conduction time up to 0.24 second. On the other hand, since anoxemia is most severe at the onset of an attack, it is difficult to explain on this basis the facts that *P-R* prolongation may appear for the first time several weeks after an occlusion and that it may persist for long periods, even permanently.

That the vagus nerve, in combination with anoxemia, may be important in the production of *P-R* prolongation is illustrated by the experiments of Greene and Gilbert.³⁶ After producing impaired *A-V* conduction in dogs following rebreathing of air with reduced oxygen tension, they were able to abolish it by cutting the vagi. We have not been able to determine whether simple prolongation in coronary thrombosis is also associated with increased vagal influence. If this is true, atropine should abolish the conduction disturbance. Administration of this drug in 3 of our cases indicates that vagal influences probably play a rôle in the depression of auriculoventricular conduction in coronary artery occlusion, but its importance should be evaluated by further study. In 1 case in which atropine gr. $\frac{1}{15}$ was injected intravenously, the *P-R* interval, which measured 0.24 to 0.28 second became more prolonged and 2:1 partial block promptly developed. This result is not so unusual as it appears to be, for the auricular rate was increased from 75 to 100 and with a damaged conduction system this rise in rate was sufficient to increase the degree of block by reducing the diastolic interval and the recovery period of the *A-V* node. In a second case, atropine gr. $\frac{1}{10}$ intravenously reduced a *P-R* interval of 0.22 to 0.24 second to 0.16 second within a few seconds, following which the sinus rhythm was replaced by nodal rhythm (Fig. 7). In a third

case, a similar dose of atropine reduced the *P-R* interval from 0.22 to 0.18 second.

Prognosis. Although patients with complete heart block in coronary artery occlusion may recover and several authors^{3,55,87} have offered a not unfavorable prognosis, this arrhythmia usually portends a fatal issue.^{22,54} In our series 4 of the 6 patients died, a mortality rate of 66.7%. But this result is not surprising when we recall that their average age was higher than that of patients without heart block, the degree of cardiac enlargement and heart failure greater and very extensive infarction usually present. In a previous investigation,^{68a} we found each of these factors associated with a rise in mortality rate.

The most significant factor leading to death in these cases of complete block complicating coronary occlusion is the slow rate of the heart which is usually under 40 beats per minute. The marked bradycardia reduces the blood flow and seriously interferes with the already disturbed nutrition of the heart, as well as other organs, an effect enhanced by the lowering of blood pressure which occurs following coronary occlusion. That patients with chronic complete block are often able to maintain adequate circulation for many years is due to the fact that there is present a compensatory increase in systolic blood pressure which is frequently 200 mm. or more. However, such a compensatory mechanism cannot develop for some time after an infarction, and the unfavorable effect of bradycardia predominates. The majority of cases of complete block described by other authors in which the rate was 40 or less also proved fatal. In the 2 cases in our series which survived, the rate was 75.

The prognosis in partial heart block with dropped beats is usually favorable,^{54,61} but also depends on the ventricular rate. Two of our 6 cases died and in both the rate was 40 to 48 beats per minute. In those who survived it was 50 to 100.

Simple prolongation of the *P-R* interval was of no prognostic significance since it did not affect the clinical course or mortality rate.

Therapy. Complete heart block, because of the marked bradycardia which it usually produces, may lead to the Stokes-Adams syndrome and, as we have seen, is very often fatal. Since an increase in the heart rate may lead to recovery, treatment to this end should be instituted in cases with rates below 40 and Stokes-Adams seizures; when there are no symptoms of inadequate circulation such treatment is unnecessary. Levine⁶¹ and Schwartz⁸⁷ have advocated the use of adrenalin for the Stokes-Adams syndrome and Schwartz particularly has had satisfactory results in increasing the ventricular rate or temporarily restoring normal rhythm. However, because of the danger of adrenalin in coronary artery disease, especially thrombosis, the drug must be used cautiously. Since the action of ephedrine is similar to that of adrenalin, the same care must be observed

in its use. During a period of syncopal attacks Schwartz⁸⁷ gave repeated intramuscular injections of adrenalin hydrochloride in doses of 1 cc. of a 1:1000 solution, until normal rhythm returned or the ventricular rate became fixed. Then ephedrine sulphate in 30 mg. doses orally was substituted and given 3 or 4 times a day.

Partial heart block usually produces no symptoms and needs no specific treatment. In those cases in which it causes marked slowing of the ventricular rate and cerebral symptoms, the treatment is similar to that for complete heart block. No therapy is required for simple prolongation of the *P-R* interval.

Atropine has occasionally been used with success in cases with disturbance in auriculoventricular conduction, caused presumably by increased vagal tone. Observers have pointed out that this drug shortens the prolonged *P-R* interval in pneumonia⁷⁰ and in rheumatic fever.¹⁶ We have already discussed its intravenous use in 3 of our cases of coronary occlusion with *P-R* prolongation. In 2 it improved auriculoventricular conduction but in the third it precipitated 2:1 heart block by increasing the auricular rate. Since simple *P-R* prolongation does not add to the gravity of the prognosis in coronary artery occlusion no treatment is required for it. In partial heart block with a slow pulse atropine may be administered in the hope that it will improve auriculoventricular conduction without increasing the auricular rate. In 2 of the cases of complete heart block reported by Schwartz⁸⁷ the injection of atropine produced a rise in ventricular rate, but this was only transitory. In a case of ventricular tachycardia in coronary occlusion reported by Salley,⁸² atropine caused a slowing of the ventricular rate from 115 to 30, with persistent complete *A-V* dissociation. Wedd⁹⁷ reported a case of coronary artery occlusion with complete heart block in which the latter disappeared 4 to 6 minutes following the injection of atropine but was succeeded by 2:1 heart block. In spite of these poor results the effect of atropine should be studied further.

An attempt to increase the heart rate with adrenalin or atropine was made without success in 4 patients of our series, 2 with complete, and 2 with partial, heart block. In the first case, complete block with a ventricular rate of 30 to 40 and coma, several injections of adrenalin were given. In the second, repeated episodes of complete and incomplete block alternated with sinus rhythm, and atropine and ephedrine were given orally in large doses. In the cases with partial block, atropine and adrenalin were administered.

The general treatment of coronary artery thrombosis we have described in several reports.^{68c, 69a, b} In summary, its purpose is to reduce the work of the heart by restricting the diet and providing complete rest in bed, employing morphine or other sedatives liberally if necessary. For some days after the attack the diet consists of small meals totalling a few hundred calories daily. This regime lowers the basal and total metabolism of the body and therefore the

work of the heart, and in addition, minimizes gastrocardiac reflexes. As the patient improves the diet is increased to 800 calories, which is continued for 2 to 4 weeks, depending on the condition of the patient. Often the patient feels well and no treatment is required other than rest in bed for from 4 to 6 weeks.

Very frequently coronary artery occlusion is followed by some degree of heart failure, which increases in spite of bed rest and restriction of fluids and salt intake. When this occurs we have found that diuretics, such as mercupurin, give very satisfactory results, and should be employed first. Oxygen is useful when there is obvious cyanosis or dyspnea. Occasionally venesection must be resorted to, particularly when pulmonary edema is present. These measures may relieve not only the heart failure but also the disturbance in auriculoventricular conduction, in the occurrence of which the anoxemia of heart failure may play a rôle.⁵ As the failure disappears the circulation to the septum and conduction through it improve.

We avoid the use of digitalis after coronary occlusion since it increases the work of the heart,³² an undesirable effect after an attack. In addition, it may initiate an arrhythmia,⁶³ such as ventricular tachycardia or auricular fibrillation. We have shown that ventricular tachycardia is rare in coronary artery occlusion; its occurrence has usually followed the use of digitalis. When *A-V* conduction is impaired the drug may be even more dangerous, since it depresses *A-V* conduction. Partial block, or if this is already present, complete block may be produced and an innoeuus arrhythmia converted into a very serious one. Since mercurial diuretics, *e. g.*, mercupurin, are efficient in the treatment of heart failure, we believe it permissible to use digitalis only when these have failed or after the acute stage of the attack has subsided.

Quinidine, too, in our opinion is a dangerous drug to use in coronary artery occlusion. It may increase the *A-V* conduction^{34,64} time, as evidenced by prolongation of the *P-R* interval. Like digitalis, therefore, it is especially undesirable when some degree of heart block already exists and its use should be limited to cases with persistent ventricular tachycardia.

Summary. 1. A complete review has been made of the *A-V* conduction disturbances in 375 cases of coronary artery occlusion with reference to their incidence, clinical, electrocardiographic and pathologic features, prognosis and treatment.

2. Simple *P-R* prolongation was common, occurring in 16% of cases; partial and complete heart block occurred in 3.2%.

3. Heart block appeared soon after the onset of the occlusion and usually lasted 1 to 2 weeks. *P-R* prolongation not infrequently appeared late and became permanent.

4. Permanent *P-R* prolongation and heart block may be the result of previous unrecognized coronary occlusion. Repeated

attacks of occlusion may progressively increase the *A-V* conduction defect.

5. The sudden onset of *P-R* prolongation as well as heart block may be the first and only sign of coronary artery occlusion.

6. Heart block, excluding *P-R* prolongation, was associated with heart failure, cardiac enlargement, previous hypertension and previous coronary occlusion. It was more common in older patients with advanced arteriosclerosis.

7. Symptoms attributable to the heart block appeared only when the ventricular rate fell to 40 or less, and consisted of heart failure or the Stokes-Adams syndrome with syncope and coma. The bradycardia can differentiate the latter from syncope and coma due to other causes, such as shock and cerebral embolus.

8. The prognosis of complete heart block was serious, because of the slow ventricular rate. Four of the 6 patients died. Partial heart block offered a favorable prognosis unless there was marked bradycardia. Simple *P-R* prolongation did not affect the outcome of an attack adversely.

9. It was confirmed that complete and partial heart block were associated with a specific cardiac lesion and electrocardiographic pattern. The anatomic basis was infarction of the posterior portion of the interventricular septum and posterior surface of the left ventricle as a result of right coronary artery occlusion. The electrocardiogram presented the *Q-3 T-3* pattern typical of posterior wall infarction.

10. The presence of profuse anastomotic channels in the interventricular septum around the *A-V* node prevents the more frequent occurrence of heart block and effects its remission when it does occur.

11. *P-R* prolongation was not associated with a specific anatomic lesion or electrocardiographic pattern. Anoxemia, heart failure, and vagal influences were probably significant.

12. The association of *A-V* block with intraventricular block can be attributed to septal infarction which involves simultaneously the *A-V* tissues and bundle-branch system.

13. The treatment of heart block is that of coronary artery occlusion in general. When there are persistent bradycardia and Stokes-Adams manifestations, adrenalin should be resorted to. The indications and effects of adrenalin, ephedrine and atropine are discussed. Digitalis, quinidine and nitroglycerine were considered contraindicated.

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KIDNEY FUNCTION AND UREMIA IN RENAL AMYLOIDOSIS.

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For many years it was believed that renal amyloidosis was not associated with renal insufficiency and that uremia occurring in the course of the disease was a rarity. The term amyloid nephrosis, applied to the condition by Fahr, has served to convey the impression that the course of amyloid disease of the kidney was similar to that of lipoid nephrosis, and, therefore, that azotemia was not to be expected. In recent years, however, cases of renal amyloidosis terminating in uremia have been reported with increasing frequency. Thus Dixon⁶ noted azotemia in 12 of 100 cases, Bell² in 11 of 65 cases, and Rosenblatt^{14b} in 8 of 87 cases. Other reports of uremia in amyloidosis have appeared in the literature by the following: Noble and Major (3 cases),¹³ Zadek (3),¹⁸ Jennings, Altnow and Higgins (1),⁸ Carey (1),⁵ Bannick and Barker (1),¹ Linder, Maxwell and Green (1)⁹ and others.

On our metabolic service we have opportunity to observe a considerable number of patients with amyloidosis, and it has, for some time, been our impression that impairment of renal function usually developed in renal amyloidosis that had existed for some time. It was believed that a review of the cases would serve to confirm or disprove this opinion.

In the present article, the cases of renal amyloidosis that either died or left this hospital between January 1, 1935, and August 1, 1937, are reviewed.

Since the introduction of the Congo Red test in 1923 by Bennhold,³ and the more recent clinical-pathologic evaluation of the test by Lipstein and Auerbach,¹¹ and by Lipstein,¹⁰ the diagnosis of amyloidosis has become relatively simple and accurate. Bennhold originally stated that an absorption of 60% or over of the dye indicated the presence of amyloid disease. Lipstein and Auerbach, however, after correlating the Congo Red absorption during life with the autopsy findings, concluded that an absorption of 90% or more of the dye was necessary to establish the diagnosis of amyloid disease.

In this study, the following criteria are used for the diagnosis of renal amyloidosis: 1, evidence of a predisposing primary disease; 2, albuminuria; and 3, a Congo Red test with an absorption of 90% or more of the dye. Occasionally amyloidosis has been reported when no predisposing illness could be found, but such cases are extremely rare. Corroborative findings of an enlarged liver or spleen, and of edema, are valuable in arriving at the diagnosis, but are, in our experience, not essential. It is common to find amyloid involvement of the liver and spleen at autopsy when these organs are not palpable during life. Cases of amyloidosis have been reported in which the kidneys alone were affected (Rosenblatt,¹⁴ Bell²).

The primary disease in all of the present cases was tuberculosis of either the lungs or bone. This is to be expected, since this hospital is a tuberculosis institution. However, even in general hospitals, tuberculosis is by far the most frequent predisposing illness; it was the primary disease in 82% of Saleeby's¹⁵ 50 cases from the Philadelphia General Hospital and in 110 of 125 cases reviewed by Rosenblatt¹⁴ at the Montefiore Hospital.

Albuminuria must be present in considerable amounts to warrant a diagnosis of amyloid disease of the kidney, and, in the selection of our cases, we included only those in which there was ++ albumin or more in the urine. Waldenström¹⁷ points out that even extensive amyloidosis may be present without albuminuria, but this, according to our experience, is extremely rare. It is impossible clinically to make a diagnosis of renal amyloidosis without the presence of albuminuria. The appearance of only a trace of albumin in the urine cannot be considered significant, since many tuberculous patients with this finding do not have amyloid disease at autopsy.

Of the patients that either died or left the hospital between January 1, 1935, and August 1, 1937, there were 189 in whom a diagnosis of amyloidosis had been made. Of this group, using the criteria previously outlined, there were 93 that could be classified as cases of renal amyloidosis. Several other cases were excluded

because, although they presented the findings of amyloid disease of the kidney, there was evidence of some other complication such as renal tuberculosis which might interfere with an accurate interpretation of the renal function. Thirty-one of the 93 patients came to autopsy and in each instance the postmortem findings confirmed the antemortem diagnosis.

TABLE 1.—RESULTS OF 2-HOUR TEST FOR RENAL FUNCTION.

No. of cases.	Maximum sp. gr. of urine.	% of cases.
8	1.024 or higher	21.0
3	1.021 to 1.023	7.8
4	1.018 to 1.020	10.5
6	1.015 to 1.017	15.8
6	1.012 to 1.014	15.8
11	1.011 or lower	29.0

—
Total, 38

Tests with a maximal specific gravity of less than 1.018 were considered to indicate impairment of renal function.

Two-hour tests for renal function were made in 38 of the 93 patients at some time during the course of their renal amyloidosis (Table 1). From this table it is seen that in 23 of these 38 patients the maximum specific gravity of the urine was under 1.018. If we consider that the normally functioning kidney should excrete urine with a specific gravity of 1.018 or higher, then 60% of these 38 patients showed evidence of impaired renal function. It should be kept in mind that in a number of these patients the renal concentration test had been carried out shortly after evidence of renal involvement had appeared, and thus it is quite probable that had the urinary concentration been determined at a later date, the percentage of cases showing impairment would have been higher.

The non-protein nitrogen of the blood was estimated in 67 of the 93 cases after evidence of renal amyloidosis had appeared. In 12 patients the N.P.N. ranged between 25 and 30 mg.%; in 20 it was 30 to 35 mg.%; and in 15 it ranged between 35 and 45 mg.%. There were 20 patients (Table 3) in whom the blood N.P.N. was above 45 mg.%. In many of the cases several blood chemistry determinations had been performed at varying intervals after the diagnosis of amyloid disease of the kidney had been made, but for the tabulations, only the last N.P.N. determination is recorded. A non-protein nitrogen of 45 mg. % or higher was regarded as definite evidence of azotemia. Twenty of the 67 cases (29.8%) showed unequivocal evidence of renal insufficiency. Eleven of these 20 patients died of uremia; the remaining 9 died of the primary disease or of complications of the primary disease before uremia had set in.

An attempt was made to correlate the duration of the renal amyloidosis and the advent of azotemia in order to ascertain whether there is a tendency, in amyloid disease of the kidney, towards progressive renal insufficiency and ultimate uremia. If the supposition

is correct that amyloid degeneration of the kidney is usually associated with an advancing impairment of renal function, then the incidence of azotemia should be in direct proportion to the length of survival after the appearance of renal amyloidosis. Consequently, the 93 cases of renal amyloidosis were divided into two groups—those that were not associated with azotemia and those that were. The cases of doubtful duration of the amyloid disease were excluded from each group. These doubtful cases included patients that left the hospital and those that showed evidence of renal amyloidosis at the time of admission so that it was impossible to determine the approximate duration of the disease. Only those cases in which the signs of amyloid disease of the kidney developed during their stay in the hospital were included.

The onset of renal amyloidosis was determined by the time at which albuminuria first appeared. This probably does not represent the actual onset of the disease since at autopsy minimal deposits of amyloid in the kidney frequently occurred when there had been no albuminuria during life. However, from a clinical point of view, the time of the appearance of albuminuria represents the closest possible approximation of the onset.

In the non-azotemic group there were 73 patients. Of these, 25 were considered to have renal amyloidosis of doubtful duration and were therefore excluded. In Table 2 are grouped the remaining 47 cases according to the duration of the amyloid disease. These patients all died of the primary disease or of complications of the primary disease. The patients who had developed renal insufficiency and died either of the primary disease before the stage of uremia had been reached or who died of uremia are also analyzed in Table 2. There was a total number of 20 cases in this group. Of these, 4 cases were excluded because of doubtful duration of the renal amyloidosis.

TABLE 2.—COMPARISON OF DURATION OF LIFE BETWEEN THE NON-AZOTEMIC CASES OF RENAL AMYLOIDOSIS AND THE AZOTEMIC CASES.

Duration of renal amyloidosis (yrs.).	Non-azotemic cases.		Azotemic cases.	
	No. of cases.	% of cases.	No. of cases.	% of cases.
Less than $\frac{1}{2}$	29	61.7	6	37.5
$\frac{1}{2}$ to 1	11	23.4	3	18.7
1 to $1\frac{1}{2}$	4	8.5	2	12.5
$1\frac{1}{2}$ to 2	1	2.1	2	12.5
2 to $2\frac{1}{2}$	1	2.1	1	6.2
$2\frac{1}{2}$ to 3	0	0	0	0
3 to $3\frac{1}{2}$	0	0	2	12.5
$3\frac{1}{2}$ to 4	1	2.1	0	0
Total	47	..	16	..

The non-azotemic cases are those dying as the result of the primary disease and not because of kidney involvement; the azotemic cases are those which exhibited renal insufficiency. As a group the azotemic cases lived longer than the non-azotemic. The inference is made that all the cases would have become azotemic, and died of uremia, if the primary disease had not been the cause of an early death.

A comparison of the two groups shows that the duration of the amyloid process was usually longer in those patients who had azotemia. Only 14.8% of the non-azotemic cases lived more than 1 year, while of those with an elevated blood N.P.N., 43.7% lived more than 1 year.

In 4 of the 7 patients in the non-azotemic group that lived more than 1 year, renal function tests were carried out at intervals of several months after the onset of the disease. The results of these tests indicated a progressive impairment of renal function in each instance, and before death the maximum specific gravity of the

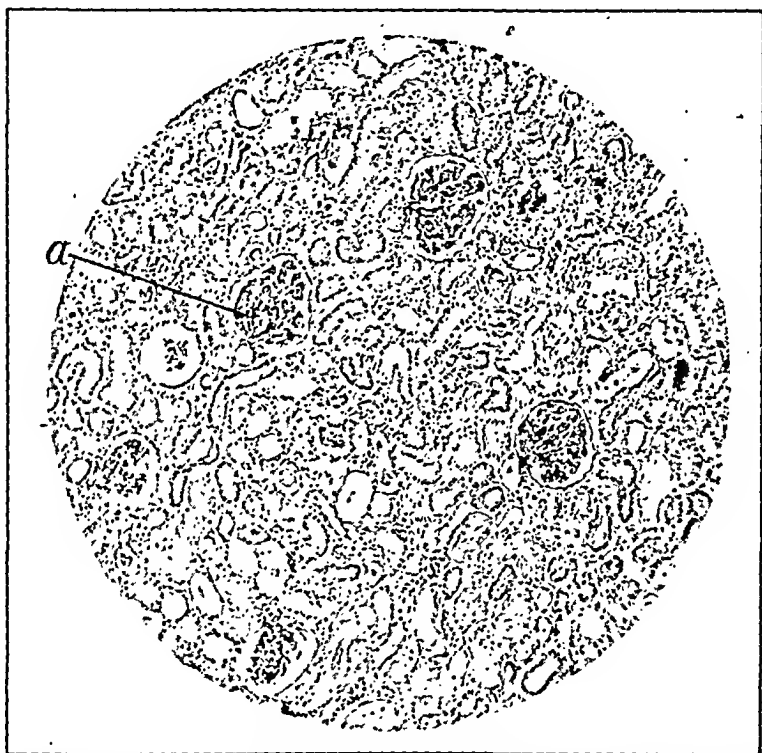


FIG. 1.—Section of kidney showing *a*, minimal amount of amyloid deposit in some of the glomerular loops. The patient died of pulmonary tuberculosis 1 month after the appearance of albuminuria.

urine was below 1.018 in all. From these results it appears that the amyloid deposition in the kidney is persistently progressive and had these patients lived longer, they would have developed azotemia.

These facts suggest that impairment of renal function advances constantly in amyloid disease of the kidney, and that the longer the individual lives, the more likely is the development of marked renal insufficiency. It is to be noted, however, that in some cases renal insufficiency manifests itself rather rapidly and in others more slowly. It is only natural to expect that the rate of amyloid deposition must vary in individual cases, probably depending upon the severity of the primary disease.

Unlike most renal conditions in which a progressive renal insufficiency occurs, amyloid disease of the kidney is usually associated with a normal or low blood pressure. The blood pressure readings in the 20 cases in which azotemia was present are recorded in Table 3. Only 3 of these patients (Cases 13, 15, and 20) can be regarded as having developed hypertension and in 2 the blood pressure was only slightly elevated. Thus it is evident that even in the presence of progressive renal insufficiency and uremia, the blood pressure in the large majority of cases remains normal or low. This finding is

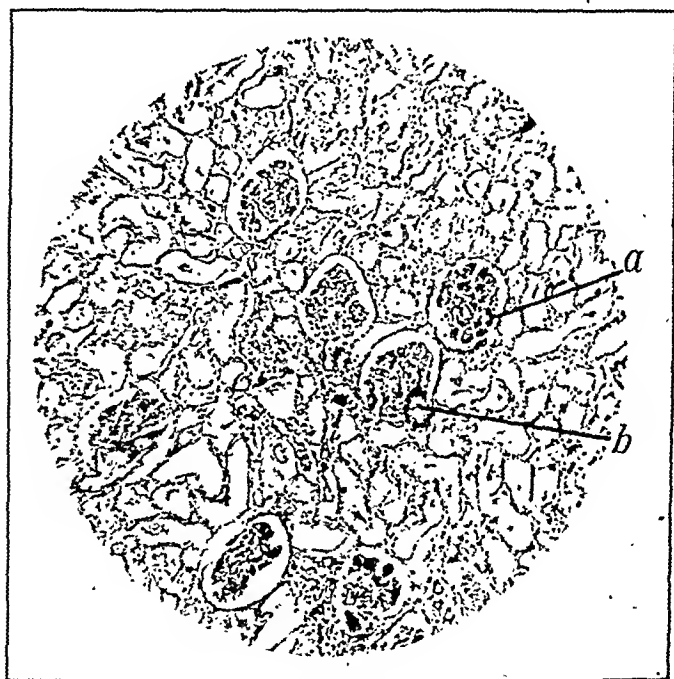


FIG. 2.—Section of kidney showing deposition of amyloid substance in most of the glomeruli *a*, *b*. Note that the amyloid involvement is more extensive than in Fig. 1. This patient died of pulmonary tuberculosis 3 months after albuminuria developed.

in agreement with that of most authors (Bell,² Dixon,⁶ Rosenblatt,¹⁴ Mosehcowitz¹²). There have been occasional reports of hypertension in cases of renal amyloidosis terminating in uremia (Jennings *et al.*,⁸ Noble and Major,¹³ Bell,² and Fahr^{7b}). It is interesting to note that in most of the cases recorded in which hypertension was present, contracted kidneys were found at autopsy, whereas in those patients that died of uremia associated with a normal blood pressure, the usual necropsy finding was the large, smooth, pale, waxy kidney.

Of the 3 patients in whom hypertension was noted, an autopsy

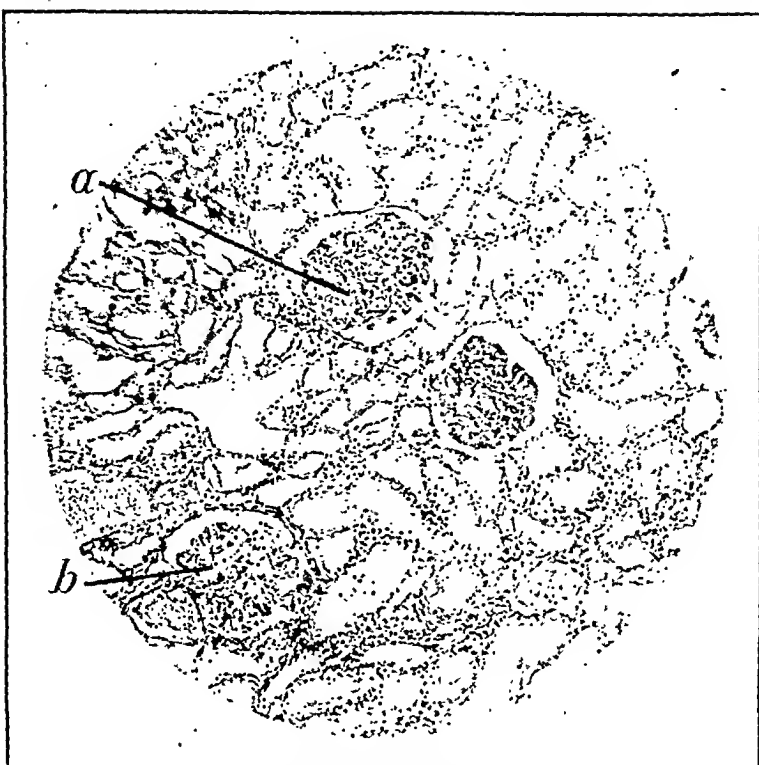


FIG. 3.—Section of kidney in which there was amyloid involvement of most of the loops of nearly all glomeruli *a, b*. The amyloidosis is more extensive in this case than in the preceding 2. The patient died of pulmonary tuberculosis 18 months after the diagnosis of renal amyloidosis was made. There was impairment of renal function as determined by the renal concentration test, but no azotemia.

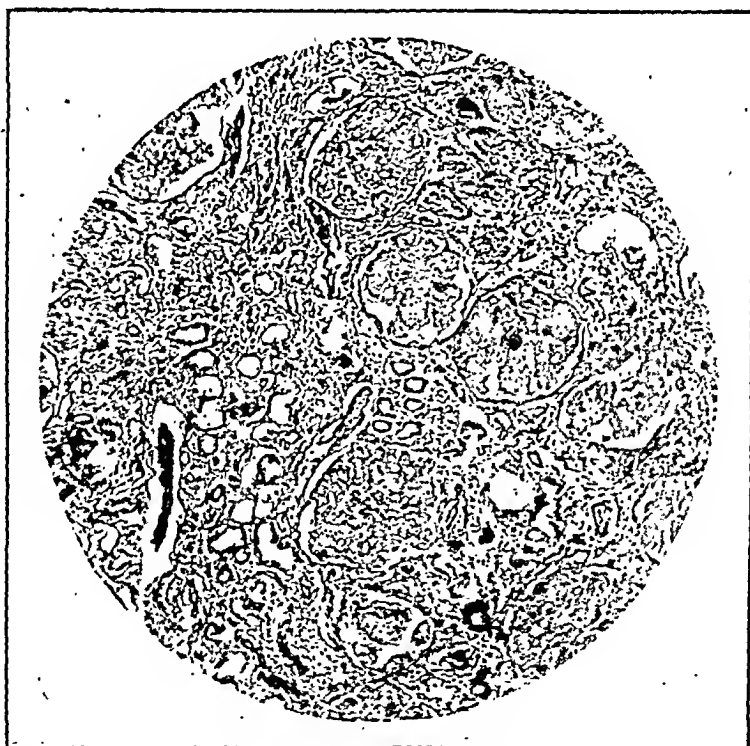


FIG. 4.—Section of kidney of a patient who died of uremia 2 years after the appearance of albuminuria. Note the extensive amyloid deposit in the glomeruli and the paucity of blood cells in the glomerular loops. There was tubular atrophy and increased interstitial fibrosis. The kidneys grossly were large, pale, smooth and waxy.

was performed on 1 (Case 20) and in this instance contracted amyloid kidneys were found.

The low blood pressure associated with amyloid disease of the kidney cannot be attributed to cachexia as Fahr^{7b} believes. In the study of our cases, blood pressure determinations had been made, in most of them, at frequent intervals throughout the course of the disease and the pressure remained consistently low in all except those recorded with hypertension. Although cachexia is marked in most patients terminally, the general condition remains fairly

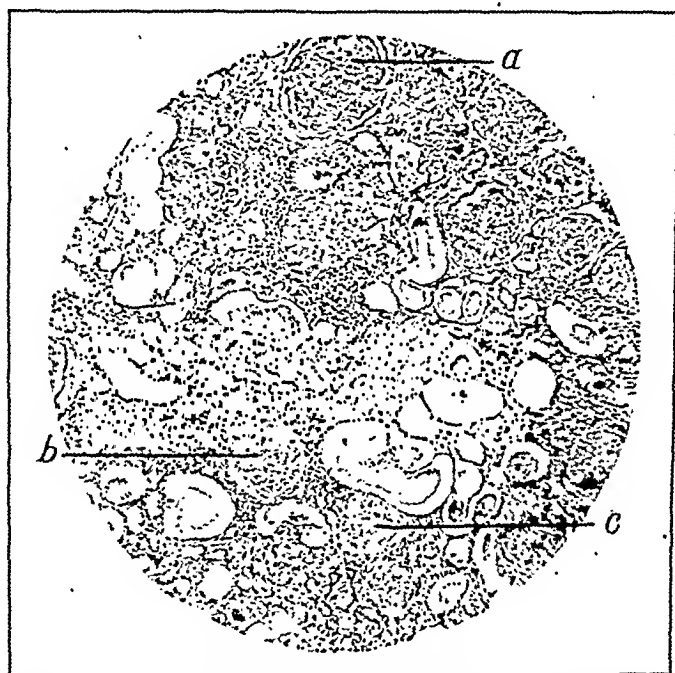


FIG. 5.—Section of kidney from a patient who died of uremia $3\frac{1}{2}$ years after the clinical onset of renal amyloidosis. At autopsy, amyloid contracted kidneys were found. Note the extensive involvement of the glomeruli and the marked tubular atrophy and interstitial fibrosis. At *a* is seen a glomerulus in which there is extensive amyloid deposition. At *b* the amyloid is being replaced by hyaline connective tissue and at *c* the amyloid has been completely replaced by fibrous tissue.

good in many until shortly before death. Nor can the normal or low blood pressure be entirely attributed to the etiologic tuberculous disease. On our wards there are patients with either essential hypertension, or chronic glomerulonephritis in whom severe hypertension is present in spite of the associated tuberculous disease.

In 9 of the patients with renal insufficiency that came to autopsy, the heart was found enlarged in 3 (Cases 10, 19 and 20). In 1 of these (Case 10) mitral stenosis was found, so that the enlargement in this instance cannot be attributed to a preceding hypertension.

Of the remaining 2 cases, 1 (Case 20) had had clinical hypertension and the other (Case 19) a normal blood pressure.

The eyegrounds in renal amyloidosis with azotemia have been observed to be normal by most investigators and we have been able to corroborate that finding. This also indicates that hypertension had not existed. The eyegrounds were examined in 7 patients with uremia and in none of these were abnormal changes noted.

It was previously believed that the amyloid kidney in patients with renal insufficiency and uremia was a small granular kidney—

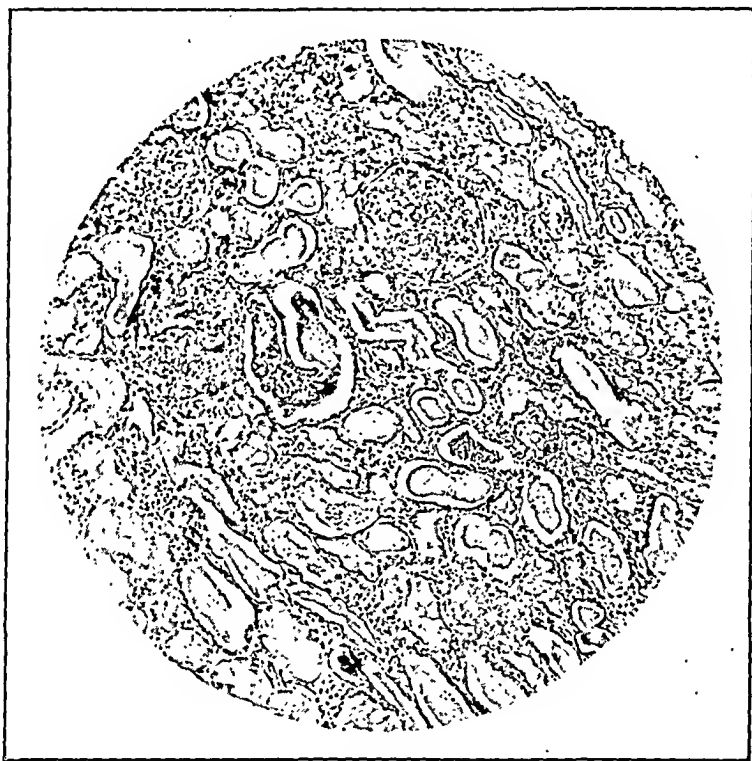


FIG. 6.—Section of kidney of a patient who died of uremia 2 years after albumin appeared in the urine. Note the large number of tubular casts. The involvement of the glomeruli by amyloid was not more extensive in this case than in other cases where azotemia had not developed. It was felt that, in this instance, uremia resulted from tubular obstruction by casts.

the so-called amyloid contracted kidney. The early writers (Senator,¹⁶ Bull⁴) claimed that the amyloid contracted kidney was not the result of pure amyloidosis, but represented a parenchymatous nephritis or an arteriosclerotic kidney, with amyloidosis superimposed. Fahr,^{7a} however, found that chronic glomerulonephritis very rarely accompanied amyloid disease, and that arteriosclerosis played little, if any, part in the contraction of the kidneys that he had observed. He concluded that the contracted kidney was the result primarily of the amyloid deposition.

In recent years, cases of amyloidosis terminating in uremia have been noted in which the kidneys at autopsy were found to be large, pale and waxy. These reports show that the contracted kidney is comparatively rare and that the large pale kidney is the common finding. In none of the 7 cases of amyloidosis with renal insufficiency in Dixon's⁶ series were the kidneys contracted. Rosenblatt¹⁴ found 1 instance of contracted amyloid kidney in 8 patients that died of uremia. In our group, of 9 cases with renal insufficiency that were autopsied, in only 1 instance was a contracted kidney noted. The combined weights of the kidneys in the patients on whom necropsy had been performed are recorded in Table 3.

TABLE 3.—SUMMARY OF CASES OF RENAL AMYLOIDOSIS WITH RENAL INSUFFICIENCY.

Case.	Age.	Sex.	Etiologic disease.	Duration of etiol. disease (yrs.).	Duration of renal amyloid (yrs.).	Blood pressure.	Blood N.P.N., mg. %.	Blood creatinine, mg. %.	Edema.	Cause of death.	Heart wt. (gm.).	Combined wt. of kidneys (gm.).
1	30	M	Pulm. tb.	4	4 m.	114/70	45	..	0	Pulm. tb.		
2	27	M	Pulm. tb.	7½	1½	110/78	46	..	0	Pulm. tb.	190	Normal*
3	32	M	Pulm. tb.	2½	1½	100/85	48	..	+	Pulm. tb.		
4	60	M	Pulm. tb.	10	4 m.	100/70	48	..	+	Pulm. tb.		
5	48	M	Pulm. tb.	2	2 m.	108/64	60	..	++	Hemoptysis	280	Normal*
6	53	M	Pulm. tb.	5	4½ m.	135/90	69	..	++	Pulm. tb.		
7	16	M	Tb. hip joint	5½	2	100/68	80	..	++	Uremia(?)	200	320
8	36	M	Pulm. tb.	5	6 m.	...	84	..	++	Empyema	290	700
9	24	F	Pulm. tb.	10	1	...	90	3.7	+	Pulm. tb.		
10	56	M	Pulm. tb.	?	?	122/72	132	6.6	0	Uremia	400	452
11	16	M	Pott's dis.	7	?	...	138	..	+	Uremia		
12	29	M	Pulm. tb.	1½	?	90/60	150	..	+	Uremia		
13	58	M	Pulm. tb.	3½	1	146/98	156	8.6	+	Uremia		
14	44	F	Pulm. tb.	9	1½	82/60	168	6.6	+	Uremia		
15	63	M	Pulm. tb.	8½	2	135/98	180	5.5	0	Uremia		
16	35	M	Pulm. tb.	10	3½	115/80	192	..	0	Uremia	270	710
17	45	F	Pulm. tb.	4	1	116/80	228	6.0	0	Uremia		
18	25	F	Pulm. tb.	6	2	96/70	240	7.5	+	Uremia	200	610
19	32	M	Tb. hip joint	?	?	100/60	240	9.8	0	Uremia	350	525
20	42	F	Pulm. tb.	14	3½	190/98	250	10.8	+	Uremia	315	280

* The kidneys were not weighed, but appeared normal in size.

Microscopically, the earliest changes of renal amyloidosis are noted in the glomeruli and in the walls of the arterioles. Bell² and others have shown that the amyloid is deposited on the intima of the glomerular capillaries and in the muscularis of the arterioles. It is also occasionally present in the basement membrane of the tubules and in the interstitial tissue. With the progression of the disease there is an increasing deposition of amyloid in the glomeruli so that eventually the entire glomerulus appears as a ball of amyloid substance (Fig. 4); it is not surprising, in these instances, that uremia should develop. Fahr^{7a} stated that even in advanced amyloidosis, the glomerular circulation may be good. However, if the process continues the capillary flow may eventually be completely obstructed. Finally the whole glomerulus may shrink and the amyloid be replaced by hyaline material (Fahr^{7a}) (Fig. 5).

The associated changes of tubular atrophy and interstitial fibrosis are probably directly due to the impaired glomerular circulation. Fahr^{7a} believes that tubular compression by interstitial amyloid or by tubular casts may account for a considerable part of the tubular atrophy in late stages, but Bell² believes this to be rare. Our studies agree with Bell on this point.

Tubular casts vary in number. In some instances, the casts are quite numerous and, in fact, may be sufficient to obstruct most of the tubules and thereby produce uremia (Fahr,^{7a} Bell²). One of our cases (Fig. 6) developed uremia apparently on this basis since there was insufficient amyloid deposition in the glomeruli to account for the renal insufficiency.

As a general rule, with increasing duration of the amyloid disease, there is a progressive deposition of amyloid in the glomeruli. This is demonstrated in Figs. 1, 2, and 3, and tends to support the clinical observation that the longer the duration of renal amyloidosis, the greater is the probability that renal insufficiency will develop. However, there are some cases in which the amyloid is deposited very rapidly, and others in which the process is a slow one.

Conclusions. Between January 1, 1935, and August 1, 1937, there were 189 cases diagnosed as amyloidosis at Sea View Hospital; of these, 93 were classified as renal amyloidosis and are analyzed in this report.

Kidney insufficiency and uremia are prone to develop within 3 years of the onset of renal amyloidosis.

Hypertension is not common in the kidney insufficiency of renal amyloidosis; when it does occur it usually accompanies a contracted amyloid kidney.

Large waxy kidneys are the ordinary finding in the uremia of renal amyloidosis; contracted kidneys are the exception.

Renal insufficiency may be produced either by shutting off of the circulatory flow in the glomeruli or by plugging of the tubules by casts.

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DIABETES INSIPIDUS WITH BIG BLADDER (CAPACITY 2 LITERS).

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An amazing instance of diabetes insipidus which caused no nuisance to the patient is worth recording. The explanation was the big bladder shown by Roentgen ray (Fig. 1).

Case History. Mr. P. W. was born in Hungary, November 11, 1905, and at 22 he came to San José where he was working his way through school when first seen. His family history revealed no developmental anomalies. He had been under observation for occasional pain in the right flank. He had polyuria without pollakiuria, a most unusual phenomenon. With regard to possible brain infections or injuries, he remembered only being told that as a young child he fell over backwards in his chair. He has never been sick in bed for a week nor had any peculiar fevers.

Bladder. The polyuria was already existent in 1913 at the age of 8 years, when it amounted to about 8 liters per day; at its worst, at the age of 15, he estimated it as 10 or 12 liters. No incontinence. No discomfort such as might be expected from the big bladder. No pain on urination. Gonorrhea denied. Frequency of urination has been at most 4 times during the day and once during the night, and generally less.

On removing a gangrenous appendix in March, 1928, Dr. H. G. Jones and Dr. T. V. Moore, of San José, made the following observations: Fluid was found coming from a multilocular cystic tumor which filled the pelvis and extended high into the abdomen on the left side. The tumor was evacuated through a small opening, yielding about 5 liters of clear straw-colored fluid. The tumor lay in front of the parietal peritoneum, and was attached above to the umbilicus and below to the bladder. They believed it to be an unobliterated embryologic urachus and to consist of 3 or 4 sections communicating with each other and with the bladder. It was thought inadvisable to attempt removal of the cyst at the time.

On August 14, 1928, the patient was seen (E. R.) and promptly sent to Lane Hospital for Roentgen ray examination. Dr. R. R. Newell's extraordinary film is reproduced in Fig. 1 and his report follows: "X-ray of bladder, injected. The bladder is very large, and continues in a pouch of equal diameter and upward and slightly to the right, above the level of the crests of ilia. The outline is smooth but slightly wavy. The clinical diagnosis of cyst of the urachus would account for this very well." And a week later: "X-ray of bladder, injected, for comparison with previous films. Another injection in smaller quantity shows the bladder well rounded out, but the sac projecting upward and the right much less distended than at the first examination. We have demonstrated some difference in elasticity of the wall of the sac and of the bladder itself, but remarkably it seems to be the sac which is more tonic." The capacity of the distended bladder may be esti-

* The lamented death of Dr. Rixford on January 2, 1938, left the manuscript to be completed with the help of his records but without his criticism.



FIG. 1.—Two-liter bladder with diabetes insipidus.

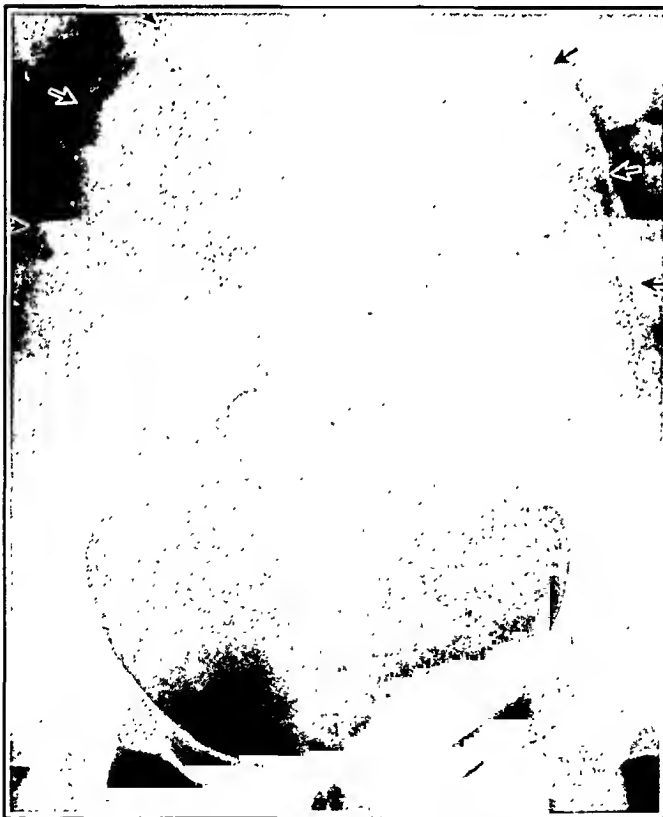


FIG. 2.—Bladder with cord tumor, capacity 2900 cc



mated from the radiogram. Let us assume that the geometric shape approximates a prolate spheroid, that is, figure generated by an ellipse revolving about its major axis; call the longer semi-axis a and the shorter semi-axis b ; then the volume wanted is $\frac{4}{3}ab^2$. On the film we measure the two diameters, multiply by $\frac{3}{4}$ to correct for magnification, and get 18.4 and 10, whence $a = 9.2$, $b = 5$. Hence the volume was 963 cc. at that time.

Operation (E. R.) was done on December 22, 1928, to determine whether there was an obstructing urethral bar or valve, or in case of finding a cyst of the urachus, then for its excision. Median incision; the bladder extended practically to the level of the navel, entirely within the peritoneum, hence not a urachal cyst. The abdomen was closed and bladder opened through a suprapubic incision, extraperitoneally; it was normal except for roughness and enormous thickening of the muscular wall such as found with an old hypertrophic prostate; the rugæ being in the upper extension of the bladder as well as the lower, and between these two parts no line of demarcation. A sound was introduced downward from the bladder into the urethra and met with obstruction, but when passed from below entered the bladder without difficulty; this suggested a congenital valve in the prostatic urethra. Cystoscopy was done, January 16, 1929, by Dr. R. L. Rigdon, with negative findings, and the next day the patient was discharged. In May, 1929, the patient wrote with gratitude reporting himself "healthy and strong."

Diabetes Insipidus. Inasmuch as the large amount of urine passed caused the patient no trouble, the amount of attention given to the symptoms had been slight. Pituitrin, 0.5 cc., had been injected once a day for 10 days in November, 1930, the urine volume was not measured but appeared unchanged; the only effect noticed was flushing of the face developing within $\frac{1}{2}$ hour and lasting 3 hours after each injection.

The 24-hour amount of urine was first measured, June 9, 1929, as 5760 cc. During the 4 days here there were successively 8332, 6851, 6494, and 5636 cc., averaging 6828 cc. The single specimens in each 24-hour period were only 4 in number, their quantity varying from 905 to 1898 cc. Evidently the bladder capacity at this time was nearly 2 liters.

The NaCl output for the first 24 hours on an unrestricted diet was 12.8 gm., then on a measured diet of C. 195—P. 75—F. 85—Calories 1845 during the next 3 days fell to 5.9, 2.7, 1.7 gm. In short, some improvement. The body weight fell from 70.3 kg. (155 lbs.) net on admission to 63.5 kg. (140 lbs.) net on discharge; a notable loss of tissue fluid.

Albumin was present in only the slightest possible trace by the heat and acetic test, while with Tsuchiya's reagent there were successively 600, 563, 468, and 396 mg. per 24 hours, as against normal of 50 to 100 mg.

Treatment. Several procedures were considered and discarded: 1, prolonged low-salt diet; 2, pituitrin subcutaneously (unsuccessful in the course stated above); 3, lumbar puncture, while said to cause dramatic decrease in output, was not done because the patient neither made complaints of his head nor showed changes in visual acuity or fields.

After-history. The patient was evidently alive on March 11, 1936, and on December 16, 1936, when physicians wrote asking for prior records; these were sent, with request for information on his condition; none was returned. Such are the difficulties of following up a remarkable condition. **Bigger Bladder.** A cord bladder may be even more monstrous. For comparison we reproduce in Figure 2 an unpublished Roentgen ray of the case reported from a different angle by Towne and Reichert.¹ The Roentgen ray report by Dr. Edward Leef reads: "Filling the entire pelvis and lower abdomen up to the third lumbar vertebra, we see a large spherical area of increased density which represents a very large, completely filled urinary

bladder." The size estimated by the same method as before, is defined by the corrected diameters 21.8 and 16.0 cm., whence the volume 2922 cc. Even greater capacity was anticipated on first comparing Figure 2 with Figure 1, but this is demonstrable as merely an optical error by noting the proportionately larger scale of the pelvis in Figure 2.

Summary. A case of diabetes insipidus which was free of discomfort owing to the storage capacity of a big bladder is reported, illustrated with a radiograph. Also, for comparison a radiograph of a less rare but even bigger bladder associated with cord tumor.

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A SYNDROME CONSISTING OF AFFECTIONS OF THE KIDNEY, STUNTED GROWTH, RICKETS AND DISTURBED CYSTINE METABOLISM.

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IN 1924,¹² the above-mentioned conditions were found occurring together in 4 cases of young children.* One may ask whether it was justified to unite the clinical, anatomic and histologic symptoms into one syndrome. Was this combination perhaps characteristic of a definite infant disease or should it be considered as the fortuitous occurrence of different diseases in the same patient?

Until very recently it seemed that in this case one had happened to come across a very uncommon coincidence of pathologic changes. But in 1936 and in the beginning of 1937,^{4,17} similar observations in infants were reported from London and from Göttingen, so that now 7 cases have been published. The latter authors were also struck by the coincidence of the above-mentioned pathologic conditions. It is worth while to ascertain once more, in the light of recent researches, the possible correlation between the symptoms.

Of the cases reported, 5 are boys, aged 21 months, 1½, 2, 3 and 16 years, and 2 girls, aged 14 months and 12 years.

These case reports now enable us to distinguish an infantile and a juvenile form.

Only twice was hydrocephalus internus diagnosed, which shows that this anomaly need not be present; perhaps the rickets accounts for it. Polydipsia, polyuria and also glycosuria have not been ascertained in all cases, and probably are dependent upon the renal affections. No histologic changes were found in the hypophysis in the cases in which this organ could be examined. During the whole

* In the beginning of this century E. Kaufmann made a similar observation with a boy of 21 months. Abderhalden¹ was able to ascertain cystinuria in 3 generations of this family.

illness, if it is accompanied by glycosuria, the blood sugar percentage is not increased. The German authors, in their case of a boy of $1\frac{1}{2}$ years, speak of renal diabetes. The English authors, in the case of their first patient, think they can explain the glycosuria by a diminished glucose tolerance.

In all cases there are serious affections of the kidney, but they do not show the same anatomic and histologic changes. In some cases, they are distinct symptoms of a very serious albuminous degeneration (nephrosis), in other cases there exists an acute, non-purulent pyelonephritis or an interstitial proliferative nephritis; in 1 case the latter disease affected the incompletely developed kidneys (boy of $1\frac{1}{2}$ years).

The stunted growth and development in early youth are very conspicuous. The 12-year-old girl is a dwarf, but this cannot be said of the 16-year-old boy. Fully developed rickets is always present, except in the case of the boy of 16, yet until his seventh year he was under treatment for this disease. Shortly before his death rachitic symptoms were not (particularly) observed, neither was the skeleton specially examined after death. In the only case where the parathyroid glands were examined (the 12-year-old girl), they appeared to be enlarged.

A surprise for pathologist and clinician is the postmortem discovery of characteristic crystalline cystine deposits in the different organs, most obvious in the spleen. In none of the cases was examination for cystinuria made, though from an observation in a 14-month-old girl it should be accepted that it can exist. At the postmortem examination of this girl cystine calculi appeared to be present in renal pelvis and ureter. In this case, however, the cystine deposits in the organs were not visible macroscopically, but only after an extensive microscopic search.

In this connection, attention should be especially given to English and American researches attempting to show the correlation between affections of the kidney and rachitic (or similar) symptoms, and between affections of the kidney and dwarfism. The term "renal rickets" and "renal dwarfism" have become established, implying that in these cases the affection of the kidney causes the rickets and the dwarfism. Fletcher,⁷ Miller and Parsons,¹³ Barber,^{3a} Shipley *et al.*¹⁸

If we inquire which affections of the kidney are found in connection with rickets and dwarfism, we see that repeatedly interstitial proliferation of the connective tissue, sometimes accompanied by slight inflammatory changes of the glomeruli, is found. In a number of cases bilateral, congenital cystic kidneys are found, in 1 case combined with an excessive proliferation of the connective tissue. In only a few cases pyelonephritis has led to a progressive renal insufficiency, combined with the above-mentioned anomalies of the skeleton. There have also been described: a bilateral hydro-ureter

and hydronephrosis with atrophy of the kidneys; renal calculi with destruction of the renal tissue and proliferation of the connective tissue; absence of one kidney, the other showing cystic degeneration; deformity of the kidneys and finally a moderate glomerular sclerosis of the kidney with extreme lipoid nephrosis combined with arteriosclerotic changes of the aorta and the small vessels.*

As to the etiology of the most frequent renal affection, namely, chronic, interstitial, proliferative nephritis, one is still completely in the dark. Worth mentioning is Welz's opinion, based upon the literature and upon two observations of his own, that incomplete development of the kidneys is primary, and that proliferation of the connective tissue is brought about secondarily by different factors.

By prolonged observation of similar cases Barber^{3b} and other authors could prove that in youth the affections of the kidney were evident many years before the changes of the skeleton, and sometimes even could be diagnosed from birth. It was natural to surmise a causal relation between these affections of the kidney and the pathologic changes of the growth of the skeleton that appeared later on. However, we should be circumspect, for injurious influences, not yet known it is true, sometimes in combination with congenital inferiority of the organs, may bring about changes of both organs in different periods.

Only in 40% of these cases is chronic, infantile, interstitial proliferative nephritis, leading to a renal insufficiency, accompanied by the above-mentioned maladies of the bones.⁹

On the other hand, the results of von Balogh² should be considered: having so injured the kidneys of young rats, that functional disorders resulted, he saw a considerable retardation of growth after from 5 to 8 weeks, as compared with healthy rats from the same litter.

"Renal" dwarfism as such is characterized by the fact that normal proportions of the parts of the skeleton remain unchanged. It may be difficult to distinguish from infantile dwarfism, when in a case of renal dwarfism there is also defective development of the secondary sex characteristics.

Rickets leads to deformities of the bones, possibly resulting in a dwarfish build. In this case, the cause of the dwarfism lies in the distortions of the vertebral column and of the lower extremities; yet *sensu stricto* this dwarfish build should not be regarded as rachitic dwarfish growth, which is the result of the delayed or defective longitudinal growth, as a consequence of serious impairment of the epiphyseal cartilages of the lower extremities, especially of the femora.

According to the descriptions, "renal rachitis" is rather changeable and variable in its pathologic aspect, though Hamperl and Wallis⁹ in 1 of their cases do not hesitate to admit that clinically

* An excellent review of the subject is given by Alfred Welz.²⁰

and pathologico-anatomically the changes of bone could not be distinguished from the changes caused by genuine rickets.

In cases of genuine rickets there is, as a rule, hypophosphatemia, the calcium percentage is normal or a little too low; in "renal rickets" it is just the reverse, for we find hyperphosphatemia and hypocalcemia. Antirachitic treatment with ultraviolet rays, cod-liver oil and vigantol with few exceptions does not give any improvement in "renal rachitis;" on the contrary, we see the disease grow worse.

Welz,²⁰ from his critical study of the literature and from his own observations, suggests that renal dwarfism should be subdivided into two forms: one with normal proportions and no deformities of the bones, and one with deformities.

Now what is the causal relation between the insufficient sclerotic kidney and dwarfism and the rachitic changes? On this subject no less than 7 hypotheses have been published. It would take too long to review them all. The theory of Hamperl and Wallis⁹ may be specially mentioned in connection with the present subject: the disturbance of the metabolism in consequence of renal insufficiency would by itself be unable to bring about the rachitic changes in the skeleton and the dwarfism, the existence of a particular disposition in the patient has to be surmised as well. These authors admit also the possibility of the same injurious agent causing the changes in both kidney and skeleton.

In the light of these recent researches it is tempting to put the renal affection in the center of the pathologic picture and to regard stunted growth and rickets as dependent upon these. Russell and Barrie¹⁷ do not hesitate to speak of one of their cases as "renal rickets;" Beumer and Wepler⁴ speak likewise of "renal" dwarfism, and in their case (a boy of 1½ years) the development of the kidneys also was retarded and an interstitial, proliferative inflammation had developed.

These authors also emphasize the resemblance of this affection and of the so-called "glycosuric dwarfism with hypophosphatemic rachitis" (Fanconi⁶).

The 3 Leyden cases, however, do not correspond to this view, as the renal changes were acute; the acute cellular pyelonephritis became manifest in a 2-year-old boy, who showed from birth defective physical development and also suffered from fully developed rickets; in the other cases, the albuminous degeneration of the kidneys did not appear to have existed for a long time, whereas the skeleton already showed symptoms of florid rickets, and the stunted growth and development of the 3-year-old boy had existed for 2 years. For the time being it will be wise to wait for more, particularly clinical data, before coming to definite conclusions. The combination of renal affections, stunted growth and rickets need not by any means be "accidental;" but it may be that in these cases both

kidneys and skeleton of the patients are inferior, and consequently when exposed to injurious influences produce the pathologic changes mentioned. In this case, functional disorders of the kidneys may intensify the detrimental influence upon the skeleton.

What causes the deposition of cystine in the different organs? This uncommon symptom is mentioned in the literature only 7 times, always in combination with the other pathologic symptoms already discussed.

The following possibilities should be considered: Cystinuria* as a symptom of "cystine diathesis" was generally regarded as being the result of incomplete destruction of the cystine; according to Brand *et al.*⁵ (cited after Beumer and Wepler⁴) the symptoms of "cystine diathesis" would be dependent upon the destruction of the cystine. Whether or not these children suffered from cystinuria, was never ascertained clinically. In 1 case, cystinuria very probably existed, judging from cystine calculi in renal pelvis and ureter (14-month-old girl). In Kaufmann's¹⁰ case, Abderhalden¹ diagnosed cystinuria in 3 generations of this family. In the other cases, the members of the family were either not examined or the examination was negative.

Cystine, as a sulphur-containing amino-acid, takes a special place in protein metabolism. It cannot be formed by the mammalian organism, consequently it must be present in the food; the growth of young animals is stunted, if cystine is absent from their food. Mörner¹⁴ claims to have proved that either all the sulphur in the protein, or the greater part of it, is bound to a group, which by hydrolysis produces cystine. Cystine is found in keratin, liver protein, products of pancreatic digestion *in vitro* and fibrin. However, according to more recent researches, there is yet another sulphur-containing amino-acid, called methionin (Müller,¹⁵ 1923, cited after Beumer and Wepler⁴), that is found in casein and other substances. In growth experiments, it can completely replace cystine, without damage to the young animal. Conversely, however, cystine cannot replace methionin (Rose *et al.*¹⁶). Cystine is a normal metabolic product, that in very small quantities is excreted in the urine.

Cystine, administered^{11,12} enterally or parenterally to young mice in large doses, impairs the renal parenchyma and causes granular (cloudy) swelling of the convoluted tubules and even necrosis of the tubuli recti of the medulla.

The possible causes of the cystine deposits in these infants are many. Considered in connection with the stunted growth, the deposits might be due to the infants not being able to assimilate the cystine; the unassimilated cystine, incompletely excreted on account of the impaired function of the kidney then crystallizing in the organs. Just as, according to some authors, polydipsia,

* Cystinuria in consequence of a serious vital autolysis of the liver, as is found sometimes in cases of acute or subacute yellow atrophy is left out here.

polyuria and glycosuria may be of renal origin, so the affected kidneys in these cases would be able only incompletely to excrete the cystine, causing thereby retention of cystine. Finally, this retention can be brought about, as in cases of cystine diathesis, by an incomplete destruction of cystine in combination with an incomplete excretion by the diseased kidneys.

Russell and Barrie¹⁷ mention the case of a 13-year-old boy, who since his early youth suffered from cystinuria and cystine calculi and later developed chronic nephritis; however, after his death no cystine deposits in the organs could be demonstrated.

Thannhauser¹⁹ is of the opinion that in "cystine diathesis" there is no absolute impairment of cystine destruction. The cystine administered with the food can still be partly used, so that this diathesis ought not necessarily to lead to general and serious impairment of growth and of nutrition.

Finally, should be mentioned the possible causal rôle played by cystine in the development of infantile renal affections, as suggested by the above mentioned experiments with young mice.

Summary. A syndrome consisting of *affections of the kidney, stunted growth, rickets and disturbed cystine metabolism* is described as characteristic of a definite disease, met in 7 children, of whom 5 are boys, aged 21 months, 1½, 2, 3 and 16 years and 2 girls, aged 14 months and 12 years.

One can distinguish an infantile and a juvenile form. Renal rickets (renal dwarfism), discussed in relation to the above-mentioned syndrome, is regarded as different from it.

The disturbance of the cystine metabolism is thus far detected only at the postmortem examination. The possible causal part played by cystine in the development of infantile renal affections, as suggested by Lewis and Lignac's experiments with young mice, is mentioned.

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A STUDY OF SILICOSIS.*

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THE present study was instituted because of the increasing importance assumed by the disabilities resulting from silicosis, and, in order to ascertain the extent to which this disease is present among ex-service men under treatment in the Veterans' Administration.

A review of the clinical data of the cases indicates the inadequacy of the occupational histories in the cases of patients suspected of having silicosis, as secured and recorded in routine hospital practice. The usual procedure is to record the occupations the patient was engaged in prior to his hospitalization without describing in detail the daily hours of work, the concentration of dust, the total time of exposure to dust, and the total period of time engaged in siliceous work. Such data are essential in establishing a diagnosis of silicosis.

In recent years, silicosis has assumed importance as a disease entity. The reason for this is the rapid industrial growth during the past quarter of a century with a resulting increase of siliceous hazards. Sayers and Jones⁵ are of the opinion that nearly 1,200,000 persons are engaged in dusty occupations in which there is a silicotic hazard. This figure applies only to the manufacturing and mechanical industries. Metal mining, quarrying, stone cutting and foundry industries are also sources of exposure. Sandblasting, grinding, polishing, and hardrock drilling in coal mines, contribute materially to the incidence of the disease.

It may be said that silicosis now constitutes the greatest single occupational hazard in the country. The seriousness of silicosis is due to the fact that tuberculosis is a very frequent complication, thus causing the silicotic to be a menace to fellow workers and to his family. It is estimated that pulmonary tuberculosis is the cause of death in 75% of silicotics.

Present Study. The present study includes a detailed analysis of the clinical, and statistical data of a group of 167 silicotic veterans, 120 of whom were alive at the time of the study and 47 were dead. Of the 47 deceased silicotics 23 had had postmortem examinations, the principal pathologic findings of which have been published elsewhere.

The largest number of the living patients were in the age group 40 to 49 years; the minimum age of the group was 37 years, the maximum age was 65 years; and the average age at the time of the study was 46 years.

* The study was planned and conducted with the coöperation of Drs. Leroy U. Gardner and H. L. Sampson of Saranac Lake, New York, and Dr. H. B. Williams of Veterans' Administration, Sunmount, New York. Assisting in the study were a number of medical officers of the Veterans' Administration. To all of these physicians the author is grateful for their splendid coöperation.

Age at Time of Inception. The age grouping of the silicotic veterans at the time of the inception of the disease shows that 50% of the total number gave a history of having acquired the disease within the age groups 30 to 39 years; and 32% within the age groups 40 to 49 years. The minimum age at the time of inception of the disease was 23 years, the maximum age was 67 years, and the average age was 39 years. Of the total number 60% acquired silicosis before the age of 40, and 40% after that age.

It would appear therefore that age *per se* is not an influencing factor, and that other factors play a more important rôle in the development of the disease. It must be realized that chronic respiratory and sinus infections are very apt to be present in the early as well as in the late periods of life, and it is disabilities such as these which predispose individuals to the development of silicosis. The onset of the disease during or after middle life is of frequent occurrence and its presence must be thought of in those engaged in siliceous occupations.

An effort was made to ascertain whether or not the type of siliceous occupation had any influence upon the age of inception of the silicotic disease. It was found that in the metal mining industry the average age at the time of onset was 39 years; in the coal mining industry the average age was 37 years; in the quarrying occupations the average age was 38 years; and among those engaged in miscellaneous siliceous occupations who incurred the disease, the average age at the time of inception was 43 years.

Correlation of Occupation With Type of Silicosis. Because of the prevailing opinion that the type of silicosis is dependent to a considerable extent upon the kind of silica dust inhaled, an effort was made to correlate these data to see whether or not it would be possible to confirm such a relationship. The findings indicate that there is no apparent tendency for any of the siliceous occupations to produce a particular type of silicotic disease.

Length of Exposure. A comparison of the periods of exposure of the living and dead silicotics indicates that, as a general rule, the exposure time in the dead silicotics was shorter than in the living cases. One may infer that the deceased silicotics were more prone to the development of silicosis than were the living cases. These findings may lend strength to the opinion held by some that there is an individual susceptibility to the disease.

It was further found that silicosis may develop after as short an exposure time as 1 year; the usual minimum time is from 3 to 5 years for the various siliceous occupations. The average exposure time in the case of the living silicotics was 13.2 years and among the deceased silicotics 12.6 years.

The conclusion is reached that in silicosis the development of the disease is dependent upon a number of factors, such as the susceptibility of the individual to silica dust, the type of dust, its concentra-

tion, as well as the length of exposure. It is believed that individual susceptibility to silica dust should be stressed more than has been done in the past, inasmuch as the data in this study point to the probability of the existence of such a factor. The individual susceptibility may be due to a number of conditions such as a preëxisting respiratory or sinus disease, pathologic-anatomic development of the nasal passages, and the possibility of an increased sensitivity to silica dust.

Duration of Disease. The clinical course of silicosis, as well as the duration of the disease, differs in various occupations and industries. The data showing the duration of life from the onset of the disease to the date of this study in the living cases, and to the date of death in the deceased cases, revealed some very interesting information. It was found that the average duration of the disease in the living cases was 9 years. It must be understood that the figures are not final, inasmuch as they represent the duration of the disease in living silicotics up to the time of this study. The average duration of the disease in the case of 30 deceased silicotics was found to be 6 years. A comparison of the data in the living and deceased silicotics shows that the duration of the disease among the deceased silicotics was shorter than among the living cases.

There are certain factors which have an influence upon the duration of the disease in silicotics. Some of these are extrinsic, such as the type of silica dust, its concentration, and the length of exposure—these determine the extent of the silicotic lesions. The other factors are intrinsic and are dependent upon the progressiveness of the silicotic disease, which is influenced by the rate of nodule formation; the presence of a preëxisting or supervening tuberculous or non-tuberculous infection; and the immunologic response of the silicotic host to the infection.

Were it not for the intercurrent infections, the duration of life in silicotics would not be materially affected. However, when infection complicates the disease, the resistance of the individual may become greatly reduced and result in a shortening of the life span. It may therefore be concluded that the duration of life in silicosis is dependent to a large extent upon the immunologic response of the silicotic to the complicating infection present in a particular case.

Life Expectancy and Survival Period in Silicosis. The data on the life span of persons who enter the different siliceous occupations showed that among 73 living cases the total survival period, which includes the period from the date of entry into the occupation to the date of the study, was from a minimum of 6 years to a maximum of 43 years; the average time was 22.1 years. In a group of 30 deceased silicotics, the shortest duration of life, that is, the shortest period from the date of entry into the occupation to the date of

death, was 8 years, the maximum duration of life was 51 years, and the average duration of life was 19.1 years.

Classification of Silicotic Disease Used in Study. For the purpose of this study, the following Roentgen ray classification (Dr. H. L. Sampson) was used:

(a) First degree silicosis: The nodulations are 2 mm. or less in diameter.

(b) Second degree silicosis: The nodulations are from 2 to 4 mm. in diameter.

(c) Third degree silicosis: The nodulations are 4 mm. or more in diameter.

(d) Conglomerate silicosis: A coalescence of the nodulations, in which the Roentgen ray shows conglomerate shadows, usually with associated emphysema. Conglomeration is due to previous trauma of the lung parenchyma, the result of bacterial invasion or lymph flow disturbance.

(e) Silicosis with infection: Characterized by silicotic nodulations in the form of Roentgen ray densities with fuzzy borders, and irregular in distribution; or shadows of mottling; these have ill-defined borders, vary in size, and lack uniformity in density and distribution.

(f) Silicosis with tuberculosis: Roentgen ray densities consist of fibrotic nodulations, fluffy and hazy in outline, with a superimposed tuberculous infection, characterized by pleuritic densities, Roentgen ray irregularities of the diaphragm, or cavity formation. The silicosis and the tuberculous infection exist more or less as separate entities.

(g) Silico-tuberculosis: This is a condition in which the Roentgen ray shows conglomerate fibrotic nodulations, pleural densities, irregularities of the diaphragm domes, or cavity formation. The lung changes are so extensive and the tuberculous and silicotic conditions are so closely interwoven that one is unable to show a separate background for either condition.

(h) Asbestosis: In the early stages the Roentgen ray findings may be described as showing a ground glass appearance in the lower parts of the lung fields. In the later stages, the haze spreads to the upper portions of the lungs with the appearance of very fine stippling that obliterates most of the normal markings. The pleural shadow is definitely thickened. A characteristic finding at times is the heart shadow which is enlarged, and, radiating from it into the lung fields is a series of heavy fibrous bands; the cardiac Roentgen ray appearance has been referred to as a "porcupine heart." Manifestations of tuberculosis and other infections in asbestosis are characterized by dense homogeneous shadows with mottling and cavity formation.

Classification of Cases. The classification of the silicotics included in this study showed that 30% were cases of silicosis of the first, second, or third degree; 11% were silicosis with infection; 42% were

silicosis with tuberculosis; 16% were cases of silico-tuberculosis; there was but 1 case of asbestosis included in the study.

Symptoms and Physical Signs. It is the general experience of clinicians that silicosis, especially in the early stages is difficult of diagnosis. Symptoms and physical signs may or may not be present, and, even if present it is necessary to support the clinical evidence with Roentgen ray findings. Even the Roentgen ray evidence is frequently obscured when emphysema is present. Accordingly, a study was made to ascertain the most frequent clinical symptoms and physical signs observed in the silicoses. It was found that these varied according to the type of silicotic disease and the character of the coëxisting complications.

In uncomplicated silicosis the most frequent clinical symptoms and physical signs noted were dyspnea, cough, chest pain, impairment of breath sounds, fatigue, râles, and loss of weight, in the order named.

The predominating clinical symptoms and physical signs noted when a non-tuberculous infection complicated silicosis were dependent upon the degree of silicosis, and the nature of the infection. Dyspnea was the most frequent symptom found; the next most frequent symptom was cough; this was followed by impairment of breath sounds, chest pain, fatigue, râles, and excessive expectoration of sputum, in the order named.

In silicosis complicated by tuberculosis the most frequent symptoms and physical signs were cough, dyspnea, chest pain, fatigue, impairment of breath sounds, loss of weight, râles, excessive expectoration of sputum, loss of appetite, and blood tinged sputum, in the order named.

Inasmuch as silico-tuberculosis is characterized by more extensive lesions than is usually seen in silicosis with tuberculosis, the clinical symptoms and physical signs are more accentuated than in the latter disease. The most frequent symptoms and physical signs of the group of cases of silico-tuberculosis were impairment of breath sounds, râles, dyspnea, cough, fatigue, loss of weight, chest pain, excessive expectoration of sputum, blood tinged sputum, and loss of appetite, in the order named.

Roentgen Ray Diagnosis of Silicosis and Its Complications. In a study of the Roentgen ray findings in uncomplicated silicosis, it was noted that the most frequent Roentgen ray evidence was accentuation of the linear markings; the next most frequent finding was beading along the course of the linear markings and at the bifurcation of the trunks; discrete nodule formation was next in frequency; and next came widening of the mediastinum. Emphysema was present in 42% of the group of 50 cases.

In silicosis with infection, the most common Roentgen ray findings in the order of frequency were mottling, widening of the mediastinum, diffuse haze or shadow extending inward from the

lateral pleura of the mid-portion of the lungs, prominence of the linear markings, beading along the course of the linear markings and at the bifurcations of the trunks, emphysema, discrete nodule formation, confluent nodule formation, and a combination of discrete and confluent nodule formation.

In silicosis with tuberculosis, the most frequent Roentgen ray findings were fuzziness and haziness of the outline of the silicotic nodules, fibrosis, caseation, mottling, and emphysema.

In silico-tuberculosis the most frequent Roentgen ray findings were fuzziness and haziness of the outline of the silicotic nodules, fibrosis, mottling, caseation, emphysema, pleurisy, and cavitation. It was noted that there was a greater incidence of pleuritic involvement in silico-tuberculosis than in silicosis with tuberculosis.

Complicating and Coëxisting Diseases. The clinical course and prognosis of silicosis are dependent to a considerable extent upon the coëxisting or complicating diseases. Silicosis *per se*, especially in the early stages, is not accompanied by very much disability. It is only when a complication supervenes that the silicotic gives evidence of disablement and an occupational handicap, and the prognosis may then become unfavorable.

Abnormal anatomic development of the nasal passages, respiratory infection, heart disease, sinus infection, or any condition which facilitates the inhalation of dust, or, which retards lymph flow, may act as a predisposing factor in the inception of silicosis. A person engaged in a siliceous occupation, who has arrested or quiescent tuberculosis, may develop silicosis earlier than usual, and after the onset of the disease, a reactivation of the dormant tuberculous disease may follow.

Heart disease complicating silicosis may cause extensive lung fibrosis which in turn may result in a strain on the heart, and may lead to an unfavorable course of the silicotic disease.

Accordingly, a coëxisting or complicating disease may affect adversely the clinical course as well as the prognosis of silicosis. Such a disease may have preceded the inception of silicosis and aided in its onset, or, it may have appeared as a supervening or complicating condition and caused a shortening of the life of the silicotic.

In the group of cases studied, it was found that the most frequent complications and coëxisting diseases were: 1, Pulmonary tuberculosis; 2, cardiovascular disease; 3, emphysema; 4, pulmonary infections; 5, bronchiectasis; 6, chronic pleurisy; 7, chronic bronchitis; and 8, dental diseases.

Pulmonary Tuberculosis. It is the consensus of medical opinion, based upon experimental evidence as well as clinical observation, that silicosis increases susceptibility to tuberculosis, which may hasten the silicotic process to a fatal outcome. It is the commonest and most important complication and is responsible for most of the

deaths among silicotics. Frequently it precedes the inception of silicosis and tends to hasten its onset.

Usually the complicating tuberculous infection arises in the advanced stages of the silicotic disease, although it frequently occurs in the early stages. When pulmonary tuberculosis appears, it is accompanied by the usual symptoms and signs characteristic of the disease.

Pulmonary tuberculosis may complicate silicosis in one of three clinical forms: As silicosis with tuberculosis; silico-tuberculosis; and as an acute bronchopneumonic type of the disease.

In the consideration of the total group of 167 cases, it was found that 97 gave evidence of pulmonary tuberculosis and 70 cases were without signs of tuberculosis, either clinically or roentgenologically. Of the 97 cases, 62 were alive and 35 had died.

Of the group of silicotics with complicating tuberculosis, the minimum length of time after exposure to silica dust before the patient gave evidence of tuberculosis was 2 years, the maximum time was 40 years, and the average length of time was 15 years.

In a study of a small group of cases in order to ascertain the period of time between the first clinical evidence of silicosis and the first signs of tuberculosis, it was found that the minimum time was 2 years; the maximum time was 10 years; and the average time was 6 years.

A study of the classification of 97 cases of silicosis complicated by pulmonary tuberculosis showed that 11% were incipient, 32% moderately advanced, 57% were far advanced tuberculosis. Tuberculosis complicated the early as well as the advanced stages of the silicotic disease.

Of the 97 cases 78 gave evidence of tuberculous disease in both lungs; in 14 the right lung was involved; and in 5 the left lung gave evidence of tuberculosis.

In a detailed study of the most common sites of the tuberculous disease it was found that of the 97 cases, in 38% all lobes of both lungs were affected; in 11% the right upper lobe was affected; in 7% the right and left upper lobes, as well as the right middle lobe; in 5% the left upper lobe; and among the rest of the cases the site of the pulmonary disease varied.

In a study of the pathologic changes found in the 97 patients with complicating tuberculosis, it was found that the largest number gave evidence of caseation and fibrosis; the next largest number showed the presence of caseation, fibrosis and pleurisy; the rest of the patients gave evidence of various combinations of pathologic changes, ordinarily seen in tuberculous disease of the lungs.

Cardiovascular Diseases. The heart may show evidence of disease in silicosis. The cardiac changes may consist, in some instances, of a slow progressive dilatation and hypertrophy, the result of an obstruction to the pulmonary circulation due to extensive fibrosis of

the lungs. The cardiac failure is insidious and brings about a train of symptoms and pathologic conditions such as chronic passive congestion of various organs, ascites, hydrothorax, dyspnea, and so on.

Of 120 living silicotics under observation, 50 (41.7%) gave evidence of cardiovascular disease. Of this number, 28 patients showed the presence of cardiac hypertrophy, dilatation, or a combination of the two conditions; 16 showed the presence of fibrosis of the myocardium; and 21 gave evidence of arteriosclerosis.

Of 24 deceased cases, who had not been autopsied, 13 showed the presence of cardiovascular disease, and of the number 6 were cases of cardiac dilatation or a combination of hypertrophy and cardiac dilatation.

In a series of 23 autopsied cases studied by the writer and reported elsewhere, it was found that the cardiovascular system was a frequent site of the disease. Hypertrophy or dilatation of the heart, or a combination of the two conditions, was found in 18 of the 23 autopsied cases. The age incidence in the group of 18 cases was from 27 to 72 years; the average age was 47.4 years. It was found that in the 18 cases, cardiac hypertrophy, cardiac dilatation, or a combination of the two conditions, was present in the early as well as in the advanced stages of silicosis.

Emphysema. Considerable difficulty is frequently experienced in recognizing emphysema. It has been shown that the most reliable means for diagnosing this condition is by lateral chest roentgenograms. There is an increase in the space between the anterior cardiac border and the anterior chest wall, due to hyperaëration of the left and right upper lobes of the lung. In addition, there is a considerable increase posteriorly of the cardiospinal space, which is represented by lung tissue of the right and left lower lobes. These two areas give evidence of increased radiability. While depressed diaphragmatic domes are common in emphysema, they are not a reliable diagnostic sign.

Emphysema is ordinarily more prevalent in the advanced stages of silicosis. However, in a study of clinical as well as autopsy material, it was found that emphysema was also quite common in the early stages of the silicotic disease. Among the group of 167 cases, 99 (59%) gave evidence of emphysema.

Pulmonary Infections. Proske and Sayers¹ hold that in general the silicotic lung is the site of bacterial infection due probably to irritation of the respiratory tissues by the inhaled dust particles; this weakens the mucous membrane and renders it susceptible to bacterial action. The toxic influence of certain dusts on the tissue may be a contributing factor. These observers state that while tuberculosis is the principal complicating disease in silicosis, other infections, such as pneumonia, lung abscess, and bronchiectasis, are frequently encountered.

In a study of the group of 167 silicotics, it was found that 56 (34%) gave evidence of pulmonary infection; this number consisted of 39 cases of chronic bronchitis, 11 cases of bronchiectasis, and 6 cases of chronic pharyngitis.

Bronchiectasis. According to Proske and Sayers,¹ bronchiectasis may be due to infection or inflammation of the bronchi. Although the latter in itself would not be sufficient to cause a widening of the bronchi, there may be an added mechanical factor in the distention due to the loss of elasticity of the bronchial wall, and the presence of pleural adhesions which draw on the bronchi from all sides and cause them to distend.

The question arises as to the manner in which the bronchi become the site of infection. It is believed that oral and dental diseases, such as gingivitis and pyorrhea, are etiologic factors. According to Proske and Sayers, silicotic individuals inhale large quantities of dust during working hours, which may become contaminated with the infectious material from the teeth and gums. The contaminated dust particles which pass beyond the ciliated epithelium of the respiratory tract, reach the alveoli, where they cause irritation, and stimulate the proliferation of the microorganisms which are usually present with the dust particles. Of the group of 167 silicotics, 11 (7%) gave evidence of bronchiectasis.

Chronic Pleurisy. Chronic pleurisy is ordinarily not found in silicosis, but appears in cases of silicosis complicated by pulmonary infection. There are localized areas of thickened pleura which are commonly seen over superficial nodulations in silicosis. These are fibrotic nodulations rather than inflammatory areas. Russell, *et al.*³ found a high incidence rate of pleurisy in silicosis, particularly in those engaged in granite and hard coal occupations. In a study of the clinical and postmortem material of silicosis in veterans, the writer found pleural involvement present in 66 (40%) of the cases.

Prophylaxis and Treatment. The treatment of silicosis is principally prophylactic. It should consist of the introduction of engineering methods to control the dust at its point of generation, and to remove the dust from the atmosphere. Studies of the working environment to ascertain the dust concentration, size of dust particles, and so on, should be made periodically with a view to reducing dust hazards to a minimum.

It is important that cases of silicosis be detected and diagnosed in the early stages of the disease, so that the subjects may take steps to avert pulmonary infection, particularly tuberculosis. It is the complicating infection which is a serious problem in silicosis, inasmuch as it changes an ordinarily favorable clinical course of silicosis to an unfavorable one, with poor prognosis. The silicotic has a comparatively normal capacity for work until the inception of the complicating infection, after which disablement and an occupational handicap follow.

For the purpose of detecting the earliest evidence of silicotic disease, persons who work at siliceous occupations should undergo periodic physical examinations, including roentgenography of the chest—this should preferably be done semi-annually.

Then too it might be advisable to apply the tuberculin test routinely at these periodic examinations so as to detect tuberculosis infection as early as possible.

The question is frequently asked whether or not the silicotic subject should be removed from his siliceous occupation when the disease is diagnosed. According to a number of observers, the silicotic disease progresses to an advanced stage, even though the subject is removed from the siliceous environment. However, Sappington found that after removal of silicotics from the siliceous exposure, 20% in the first stage of the disease progressed; 40% in the second stage; and all of the silicotics in the third stage of the disease gave evidence of progressive silicosis. Accordingly, it would seem that in order to hold the disease in abeyance, prolong the life of the silicotic, and extend his occupational usefulness, it is essential that the disease be diagnosed in the early stages and, if practicable, the subjects be reassigned to less dusty work. It is particularly important that silicotics with complicating tuberculosis be removed from their dusty environment so that employees working in close proximity may be protected from infection.

Another problem which deserves consideration is the hospital treatment of silicotics. Patients with uncomplicated silicosis should not be treated in tuberculosis sanatoria because of the danger of exogenous infection; they should preferably be treated in general hospitals.

Mortality Among Silicotics. In a study of anthraco-silicosis in Pennsylvania, made by the U. S. Public Health Service,⁴ it was found that the mortality from respiratory diseases was much greater among the miners than in the general adult population of the country. Russell² states that the influence of dust on the mortality from tuberculosis is clearly demonstrated in the statistics of the granite industry. The data show that as a result of the excessive dust created by the use of pneumatic tools, the tuberculosis death rate had increased rapidly, from 1.5 per 1000 in the 1890-1894 period to 19.5 per 1000 in the 1924-1926 period. In a study of the mortality statistics among Barre, Vermont, granite workers, Russell found that there had been an excessive death rate from pneumonia and other respiratory diseases. It is a well known fact that while in recent years the death rate from pulmonary tuberculosis in the general population has been reduced, there has been an increase of the tuberculosis death rate during the same period among workers in dusty trades.

Of the group of 167 silicotics, 47 were reported to have died, 30 of the 47 cases died within the age period, 40 to 49 years. The mini-

imum age at the time of death was 27 years; the maximum age was 72 years; and the average age was 45.6 years.

In a study of the duration of the silicotic disease in the group of silicotics who had died, it was found that the minimum duration was 6 months; the maximum duration was 16 years; and the average duration was 6 years.

Summary and Conclusions. 1. Silicosis is the chief occupational disease in this country. The seriousness of silicosis is due to the fact that it is conducive to the inception of pulmonary tuberculosis. Tuberculous silicotics are a source of danger to their fellow workers as well as to members of their families, because of the ease with which tuberculous infection is transmitted. The disease results in a great economic loss to society.

2. A study of the classification of silicotic disease in a group of 167 veterans showed that 30% were classified as first, second, or third degree silicosis; 11% were cases of silicosis with non-tuberculous infection; 42% were cases of silicosis with tuberculosis; 16% were classified as silico-tuberculosis; and 1 case was diagnosed as asbestosis.

3. The various siliceous occupations act differently in causing silicosis. The differences are due to a number of factors such as the silica content of the dust, the size of the silica particles, variation in the time of exposure, the presence of organic or non-siliceous dusts mixed with silica, and the probability of the existence of an individual susceptibility.

4. In the group of cases studied, it was found that the most frequent complications and coëxisting diseases were pulmonary tuberculosis, cardiovascular disease, emphysema, pulmonary infections, bronchiectasis, chronic pleurisy and dental diseases.

5. In a study of the classification of the 97 cases of silicosis complicated by tuberculosis, it was found that in 11% the tuberculous disease was classified as incipient; in 32% it was moderately advanced; and in 57% far advanced.

6. The cardiovascular system may show evidence of disease silicosis. The abnormal cardiac changes are characterized by a progressive dilatation and hypertrophy due to obstruction of the pulmonary circulation, the result of extensive fibrosis of the lungs. Of 120 living silicotics, 50 (41.7%) gave evidence of disease of the heart or blood vessels; of this number 28 showed the presence of cardiac hypertrophy, dilatation, or a combination of the two cardiac conditions; 16 showed the presence of fibrosis of the myocardium; and 21 gave evidence of arteriosclerosis. Of 24 deceased silicotics on whom no postmortem examination was done, 13 showed the presence of cardiovascular disease, of which number 6 were cases of cardiac dilatation, or, a combination of hypertrophy and cardiac dilatation. In a series of 23 autopsies on silicotic subjects and reported elsewhere by the writer, hypertrophy or dilatation of the

heart or a combination of the two conditions was found in 18 instances. These cardiac conditions were found in the early as well as in the advanced stages of silicosis, also in silico-tuberculosis.

7. While tuberculosis is the principal complicating infection in silicosis, other infections, such as pneumonia, lung abscess, and bronchiectasis, are frequently encountered. Upper and lower pulmonary tract infections were found in 56 (34%) of the group of 167 silicotics; there were 39 cases of chronic bronchitis, 11 cases of bronchiectasis and 6 cases of chronic pharyngitis. Chronic pleurisy was present in 66 (40%) of the number; this condition is ordinarily not found in uncomplicated silicosis, but in silicosis with a complicating infection.

It is desired to acknowledge the technical assistance rendered in this study by A. Bamberg and E. K. Stone of the Research Subdivision, Veterans' Administration.

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CONTRALATERAL SPONTANEOUS PNEUMOTHORAX COMPLICATING ARTIFICIAL PNEUMOTHORAX.

WITH A REPORT OF TWO CASES.

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THE occurrence of superimposed spontaneous pneumothorax during the course of pneumothorax treatment is not an infrequent complication, but a review of the literature shows that contralateral spontaneous pneumothorax complicating artificial pneumothorax is very rare.

Dunham² (1926), reported a case of spontaneous pneumothorax occurring in the contralateral lung during the course of artificial pneumothorax with complete recovery. The diagnosis was made by fluoroscopic and radiosopic examinations, the patient presenting no symptoms whatsoever. He states that prior to this date, review of the literature failed to disclose such a case on record.

Burrell¹ (1932), in a report on 671 pneumothorax cases in which a total of 10,889 punctures of the pleura were made, mentions 3 cases which developed contralateral spontaneous pneumothorax as a complication of artificial pneumothorax with fatal results.

Stephani⁵ (in 1936), reported a case of contralateral spontaneous

pneumothorax complicating artificial pneumothorax, the diagnosis being made by radioscopic examination. The patient stated that he had a transitory pain in his chest a few days previously, but that there were no other symptoms. The spontaneous pneumothorax was absorbed in 3 months. The patient made a good recovery.

Over a period of 5 years, 1933-1937, covering a series of 877 pneumothorax cases in which 34,789 pleural punctures were made, we were able to find only 2 cases which developed contralateral spontaneous pneumothorax.

By a spontaneous pneumothorax, we mean a pneumothorax which is not brought about by external factors either accidentally or for therapeutic reasons.

Pulmonary tuberculosis is probably the most frequent primary cause. Other exciting factors which may produce this condition are lung abscess, gangrene, bronchiectasis, empyema, emphysema, and foreign body.

The direct causes of spontaneous pneumothorax are: 1, Rupture of an emphysematous bleb; 2, perforation of a cavity into the pleural space; 3, rupture of a subpleural tuberculous lesion.

We differentiate three types of pneumothorax. 1. In the closed type the manometer, reading reaching a certain positive pressure, remains constant, showing that no more air is entering the pleural space. 2. In the open type, the manometer reading remains constant, fluctuating from a certain positive to a certain negative pressure even after air has been aspirated. 3. In the valvular type, the manometer readings show a constantly increasing positive pressure.

Rubin⁴ states that males are more often affected than females, the ratio being about 4 to 1. This is usually explained on the basis of increased effort and strain in the male.

Spontaneous pneumothorax may be complete or partial, depending upon the size of the perforation into the pleural space and presence of adhesions. The signs and symptoms presented by the patient will depend upon the following factors: 1, rapidity of onset; 2, types of pneumothorax—whether closed, open, or valvular; 3, size of perforation into the pleural space; 4, presence of adhesions; 5, amount of collapse on contralateral spontaneous pneumothorax side; 6, amount of collapse already present on the opposite pneumothorax side.

A consideration of the above-mentioned factors explains the presence of a spontaneous pneumothorax in some cases which do not complain of pain, shock, or dyspnea. The diagnosis is made in these cases by fluoroscopic and radioscopic examinations.

Case Abstracts. CASE 15,730.—J. M., white longshoreman, aged 35. *Family history:* Negative for tuberculosis. *Past history:* Pneumonia in 1928.

Patient was admitted to the Sanatorium April 23, 1937, with a 6 months'

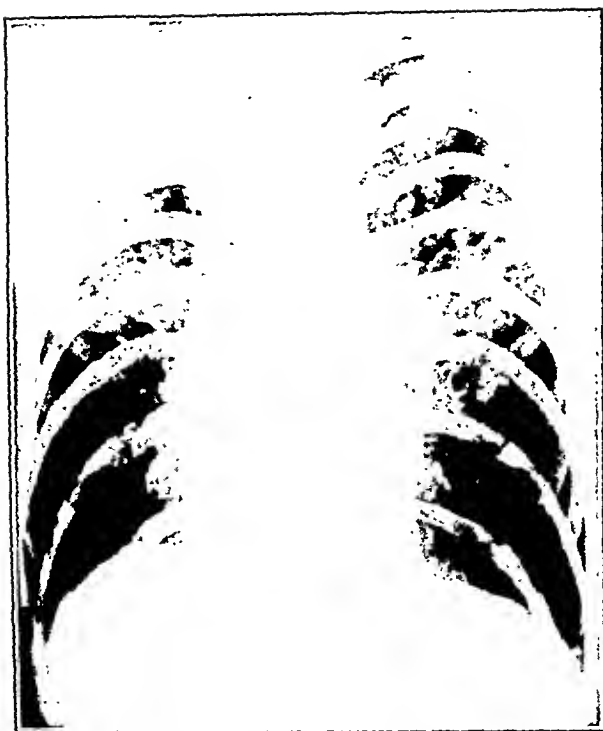


FIG. 1.—(Case 1). Roentgenogram on admission showing infiltration and cavitation of the right upper lung field and infiltration of the left mid-lung field.



FIG. 2.—(Case 1). Roentgenogram showing partial collapse of both right and left lungs with adhesions. Spontaneous pneumothorax has occurred on the left side. Note how the cavities on the right side are brought into view after the induction of artificial pneumothorax.



FIG. 3.—(Case 2). Roentgenogram on admission showing marked infiltration of the upper half of the right lung field with some infiltration of the left upper lobe at the periphery.

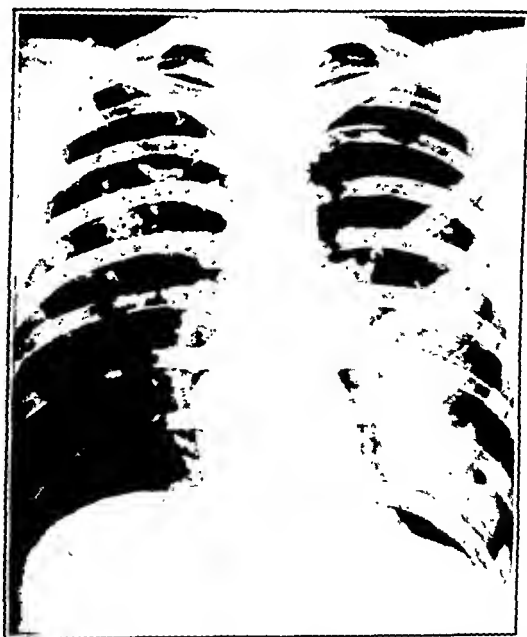


FIG. 4.—(Case 2). Roentgenogram showing partial collapse of both right and left lungs with adhesions. Spontaneous pneumothorax has occurred on the left side. Note the marked pneumonic process in the left lower lobe.

history of moderate cough and expectoration of 3 ounces yellow sputum daily; no history of streaking nor hemoptysis. Two months prior to entry he had an attack of pleurisy on the right side for which he was treated at home by his local physician.

One month before entry he began to complain of weakness, moderate dyspnea on exertion, loss of strength, loss of appetite and 26 pounds in weight (in past year), and occasional night sweats.

On admission, the temperature ranged from 97.2° to 101° F., the pulse from 80 to 110 per minute, and respiratory from 18 to 22. The sputum was positive for tubercle bacilli. Sedimentation rate 30 V. C. (Cutler Method). Weight, 114 pounds.

On examination, one noted a poorly developed and nourished, prematurely gray male, with negative physical findings except of the chest. Examination of the right chest revealed signs of infiltration over the upper half with signs of cavitation over the infraclavicular region anteriorly and supraspinatus area posteriorly. Examination of the left chest revealed signs of infiltration in the mid-lung region. Roentgenogram reports confirmed above physical findings.

The case was presented at conference, and it was the consensus of opinion that pneumothorax should be instituted on the right side. On May 3, 1937, this was begun with an initial reading of -4-7 and a final reading of -2-6 after the injection of 300 cc. of air. Refills were made twice weekly, the amounts ranging from 300 cc. to 550 cc. of air, with final readings never higher than -1-4. Frequent fluoroscopic examinations were made to check the amount of collapse, which was progressing quite favorably. Clinically, the patient showed a good deal of improvement.

On May 22, 1937, the patient developed a sudden, sharp, agonizing pain in the left chest. He was found sitting up in bed, very dyspneic, cyanotic, in profuse sweat, with a fast, thready pulse.

A quick examination of the chest showed that there was hyperresonance over the left chest with distant breath sounds. Time was not taken to localize the exact position of the heart because of the patient's poor condition. Inasmuch as there was no time to obtain a pneumothorax outfit, a standard 2-inch 15-gauge needle was inserted into the left pleural cavity, and air began to escape under pressure. The patient obtained immediate relief, and as soon as his condition improved, the needle was removed.

About 7 hours later, the patient became short of breath, and inasmuch as there was more time and the condition of the patient permitted, a pneumothorax outfit was taken to the bedside. The initial reading in the left pleural cavity was found to be +4-4. After removing 600 cc. of air, the patient was greatly relieved, and a final reading of -1-8 was obtained.

Fluoroscopic examination and roentgenogram confirmed the diagnosis of spontaneous pneumothorax on the left side.

Air was removed on 3 other occasions, the amounts ranging from 150 cc. to 400 cc.

In view of the disease in the left lung, it was thought advisable to keep a certain amount of collapse. Consequently, refills were given once weekly on the right and left sides. Negative final readings were maintained on both sides on all refills. Frequent fluoroscopic examinations were made to check amount of collapse. In spite of repeated warnings as to the seriousness of his condition, the patient persisted in taking poor treatment and continued to be uncoöperative.

On August 1, 1937, patient had a massive pulmonary hemorrhage and died. Postmortem examination could not be obtained.

CASE 15,516.—W. H., male, white truck driver, aged 27. *Family history:* Negative for tuberculosis. *Past history:* Three attacks of pleurisy left side.

Patient was admitted to the Sanatorium December 7, 1936, with a

6-months' history of cough and expectoration of 2 ounces yellow sputum daily. No history of streaking nor hemoptysis.

In addition, the patient complained of marked hoarseness for the past 3 months. No dysphagia nor soreness of throat. Slight loss of appetite and loss of 13 pounds in weight in 6 months.

On admission, the temperature ranged from 97° to 99.2° F., the pulse rate from 70 to 90, and respiratory rate from 20 to 24. The sputum was positive for tubercle bacilli. Sedimentation rate 23 D. C. (Cutler Method). Weight, 132 pounds.

On examination, one noted a fairly well developed, somewhat undernourished male, in no apparent distress. His speech was markedly hoarse. With the exception of the chest and laryngeal findings, the physical examination was negative. Examination of the right chest revealed signs of infiltration most marked over the upper third with signs of cavity over the infraclavicular region anteriorly and supraspinatus area posteriorly. Examination of the left chest revealed signs of infiltration at the apical region. Roentgenogram reports confirmed the physical findings. Laryngologist made diagnosis of tuberculous of the larynx.

The patient did fairly well on strict bed rest until April 15, 1937, when he had a hemoptysis of 5 ounces. As signs of cavitation were present on the right side in addition to its being the most diseased side, pneumothorax was instituted with an initial reading of -5-10. After injecting 600 cc. of air, a final reading of -2-6 was obtained.

Refills were given twice weekly, and this form of therapy prevented further hemoptyses, although the patient had blood-streaked sputum on several occasions. Frequent fluoroscopic examinations were made to check amount of collapse.

On June 2, 1937, patient developed a severe pain in the left chest, became somewhat dyspneic with an elevated and thready pulse. No cyanosis was present. Examination of the chest revealed hyperresonant note over left chest with distant breath sounds. No displacement of the trachea nor heart could be ascertained. Pneumothorax outfit was brought to the bedside, and needle was inserted into the left pleural space. The initial reading was +2-6. After removing 350 cc. of air, the patient was greatly relieved, and when the final reading of -2-8 was obtained, the needle was withdrawn. Fluoroscopic examination and roentgenogram confirmed the diagnosis of spontaneous pneumothorax on the left side.

No further removal of air was necessary from the left side. In view of marked pneumonic process, which had developed at the left base, it was thought advisable to keep up a partial collapse of the lung. Refills were given once weekly on both sides, the amounts ranging from 100 to 200 cc. of air, with no final reading higher than 0-8 on either side.

The patient's throat condition, despite strict silence and chaulmoogra oil treatment, became worse, with development of marked dysphagia. Patient became much weaker, due to inability to swallow anything, and expired July 23, 1937.

AUTOPSY revealed the body of a 27-year-old, emaciated, white male.

In order to confirm the diagnosis of air in the pleural cavity, a quantity of water was placed between the chest wall skin flap and the intercostal musculature. Then a stabwound was made through the water into the pleural space. Air bubbled up through stabmarks in the intercostal spaces.

Left pleural cavity: Partial collapse of the lung was seen. A firm, thick, fibrous adhesion binding the apex to the chest wall, and 2 or 3 thick adhesions at the base were present. Right pleural cavity: Lung was found to be partially collapsed. A few thick, fibrous adhesions binding the apex and one corner of the base of the lung to the chest wall were seen. The pericardial and peritoneal cavities were negative.

Left lung: Weight 980 gm. A large part of the anterior surface was covered by a thickened, dull, pigskin-like layer of fibrin. Same appearance was seen on the lateral border of the lung.

The interlobar fissure was obliterated by fibrous adhesions. The pleura was somewhat thickened, but smooth and fairly shiny. Everywhere the underlying lung was felt to be lumpy and nodular. Grayish-white nodules, 2 to 3 mm. in diameter, and conglomerations of nodules were seen beneath the pleura. Several areas about 2 cm. in diameter were easily indented by light touch. These were seen on section to be cavities beneath the pleura. The cut surface of both lobes had a grayish color and almost solid with small, grayish-white nodules about 2 cm. in diameter. There were several cavities from 0.5 to 2.5 cm. in diameter, some thick and others thin-walled, lined with shaggy necrotic membranes, and containing rather thick, yellow, purulent material. Many of these cavities connected with branches of the bronchi. There was a large, ragged cavity near the hilus in the base of the upper lobe about 3 cm. in diameter.

Right lung: Weight 900 gm. The pleura was slightly thickened over the entire lung, and smooth except under the few thick adhesions at the apex and base. Most of the lung felt lumpy and nodular to the touch.

The cut surface was grayish-red with many small, grayish-white nodules about 2 mm. in diameter. Heavy strands of white, fibrous tissue extended throughout the upper lobe, replacing much of the lung substance. There were a few cavities of 0.5 to 1.5 cm. in diameter in the upper lobe containing grayish-green, purulent material.

The bronchial branches in the middle lobe were dilated terminally. The lower lobe contained many nodules, a small amount of fibrous tissue, and a few small cavities. The bronchial mucosa was moderately congested. The bronchi contained a small amount of gray, mucopurulent material.

The rest of the postmortem examination was essentially negative with the exception of the larynx, where 3 shallow ulcers were found on its posterior aspect.

Anatomic Diagnosis: Left pneumothorax. Right pneumothorax. Bilateral fibrocaseous pulmonary tuberculosis with cavitation. Old fibrous pleuritis. Bronchiectasis of right middle lobe. Tuberculosis of the larynx.

What effect the presence of artificial pneumothorax had in the production of the contralateral spontaneous pneumothorax is difficult to say.

Matson, Matson, and Basaillon,³ among others, have pointed out that the end results of pneumothorax therapy are less dependent upon the status of the contralateral lung than they are upon the character of the collapse and the type of disease in the more diseased lung.

There is no doubt that the contralateral lung is forced to more activity when the opposite lung is undergoing collapse therapy.

We are of the opinion that the presence of artificial pneumothorax merely hastened the contralateral spontaneous pneumothorax. In all probability, the condition may have occurred even without the presence of artificial pneumothorax on the one side.

Summary. 1. Considering the number of artificial pneumothoraces that are performed today, it is surprising to see the rare occurrence of contralateral spontaneous pneumothorax as a complication of artificial pneumothorax. Review of the literature reveals 5 such cases.

2. In our series of 857 pneumothorax cases in which 34,789 pleural punctures were made, only 2 cases developed the condition.

3. A report of the 2 cases is presented with postmortem findings on 1.

4. The complication may not in itself be fatal if the condition is diagnosed early enough and proper treatment instituted.

5. We believe that it is advisable to keep a certain amount of collapse on the contralateral spontaneous pneumothorax side if the lung shows evidence of disease by past physical examination and roentgenograms. On the other hand, if the lung is normal, then it may be allowed to reëxpand.

6. Frequent manometric readings and fluoroscopic examinations are of the greatest importance in these cases.

I am grateful to Dr. John A. Foley, Chief of Staff, and members of the Staff for valuable information rendered in preparation of this paper.

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THE RÔLE OF CERVICAL NERVES IN FACIAL SENSATIONS AND THE QUANTITATIVE DISTURBANCE OF SENSITIVITY IN MAJOR TRIGEMINAL NEURALGIA.*

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IN the light of our present knowledge it seems almost unbelievable that only 125 years have passed since Bellingeri² first questioned the belief, then held, that the facial and the trigeminal nerve shared equally in the sensory as well as in the motor innervation of the face. This question remained unanswered until Bell^{1a,b} published his brilliant experiments in 1821. He sectioned in a donkey the fifth nerve on the one side, the seventh on the other side, at their entrance into the face, and demonstrated that the face lost its sensitivity on the side of the first operation, its motility on the side of the second. One year later Fodéra⁵ confirmed this observation, dividing the root of the fifth nerve close to the brainstem, a procedure to which Magendie⁹ did not fail to affix his name in the following year. With these investigations the fundamental question of the sensory innervation of the face was answered.

* Read before the Philadelphia Physiological Society, February 21, 1938.

Since then new problems have arisen which still call for solution. Some of them are especially important to neurologists and neurosurgeons because of the practical consideration incident to the diagnosis and treatment of major trigeminal neuralgia. Important among these are the degree of overlap between the cervical and trigeminal nerves and the possible responsibility of the cervical nerves for the residual sensibility of the face after section of the trigeminal nerve.

A few years after having completed his first series of extirpation of the Gasserian ganglion, Fedor Krause⁸ reported that in some of his patients a certain degree of tactile sensitivity was present in the face although pain sensation was gone. Cushing³ questioned the complete removal of the ganglion, whereupon Krause deposited the intact ganglion on the speaker's table asking where, in Cushing's opinion, should the fibers run which should account for the preserved touch sensation.

This lively controversy provoked careful investigation in two directions. Zander¹¹ and Frohse⁷ traced the terminal ramifications of the nerves emerging from the cervical roots into the face, using gross anatomic methods. Zander demonstrated that the filaments of the cervical nerves were present in all but the central portion of the face. This small central area represents what we call the pure trigeminal field. In addition, Frohse⁷ showed that a considerable degree of variability existed in the territories supplied by each division of the fifth nerve and by the cervical segments. Cushing,^{3b} on the other hand, using horse hair, pin and the faradic current, examined the cervico-trigeminal borderline and found here that Sherrington's law of overlap was not valid, at least not to its full extent. Sherrington had proved that every territory of the body was innervated by three posterior roots and that destruction of any one of them produced almost no loss of sensibility. In contrast to this fact, Cushing^{3a} showed that section of the fifth nerve as well as of the cervical roots produced a complete anesthesia of the corresponding fields which were mutually complementary; that is with the methods available at that time. In the monkey, however, Sherrington¹⁰ was able to demonstrate a considerable cervico-trigeminal overlap, using his method of residual sensibility. The situation is complicated still further by Dandy's⁴ claim that by cutting four-fifths of the trigeminal root close to the medulla touch sensation may be largely preserved over the face though sensation of pain is lost.

Although all these problems urgently required solution, no attempt has been made in the last 20 years to attack them with the tools of contemporary neurophysiology.

The material presented here was based on 50 patients suffering from major trigeminal neuralgia. They were examined repeatedly on the normal and abnormal sides and on the latter both before and

after subtotal resection of the trigeminal sensory root with v. Frey's graduated hairs and thorns and Head's algesimeter. In addition, threshold and excitation time to electrical stimulation were determined both for touch sensations (described as similar to a knock) and for short pain sensations. Condenser discharges and electrodes of 1 or of 10 mm. diameter were employed. The smaller electrode was applied directly on the touch or pain points. With the latter, 513 determinations of the threshold and 929 of the excitation time provide sufficient material for statistical treatment. Ten normal persons served as additional controls.

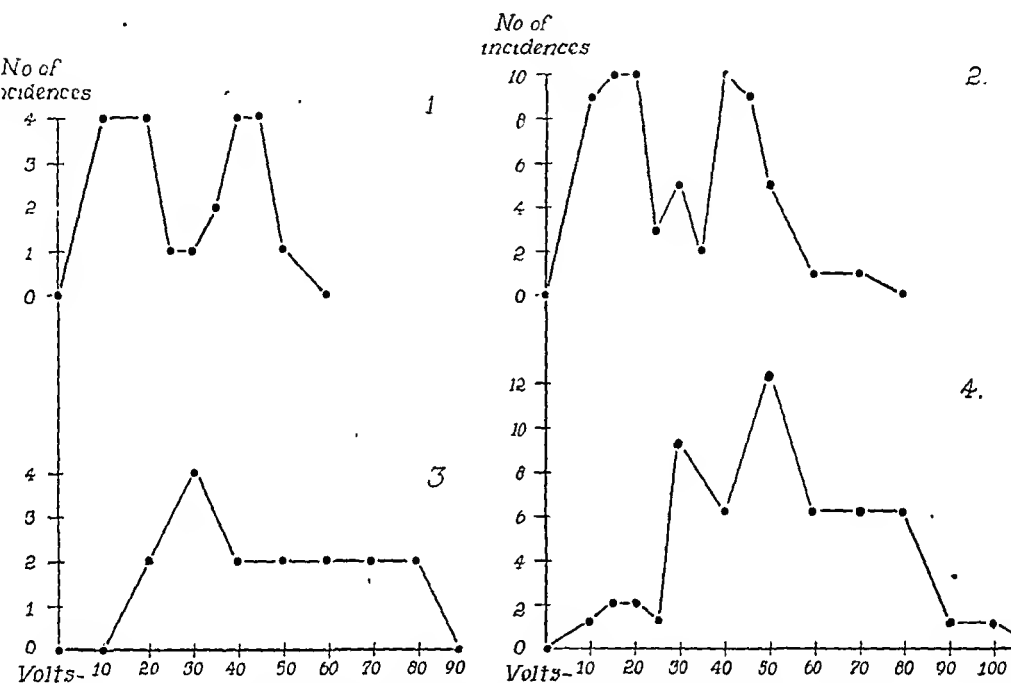
Two factors hindered the evaluation of this large mass of material. Although the surgeon attempts to divide just those fibers of the trigeminal root that supply the aching portion of the face, there is no accurate way of knowing whether he may not have destroyed a greater or lesser number of fibers in a given patient. The other source of perplexity is connected with the observation that even in normal individuals the threshold readings of adjacent touch points within a 1 sq. cm. area of the same peripheral division varies from 1 to 5 milliamperes during an examination.

For these reasons, I preferred to disregard single patients for the time being and to treat my material collectively with mathematical methods, hoping to find a common denominator. Frequency curves were drawn, plotting the *threshold values of touch points* on the abscissa against the number of incidences on the ordinate. The first graph (Fig. 1) shows the figures resulting from electrical stimulation of the touch points within an area of 4 sq. cm. in the second division of the fifth nerve on the normal side of a person suffering from trigeminal neuralgia. Figure 2 represents the aggregation of values from all three trigeminal divisions in 10 normal individuals. Both these curves are similar in their general characteristics. They show two maxima, one between 15 and 20 volts, the other between 40 and 45 volts. The corrected standard deviations for the mean values of 17.5v and 41.3v are 6.9 and 7.1 respectively, with a significant difference between the two coefficients of variation. The frequency relation between the incidence of these two values is approximately 1:1 in the first and second division of the fifth nerve, but 1:2 in the medial portion of the third division, and 1:3 in its external part.

At first glance the presence of two maxima seems astonishing but this is not entirely unprecedented. Franz⁶ examined the face of normal persons with v. Frey's hairs and found that 50% of the touch points were detectable with hairs of 0.081 gm. while the rest required 0.24 gm. for detection. I resorted to this method to find out whether the above mentioned distribution of touch points could be confirmed in single persons. Not more than 4 persons were available for study, on whom the result could be considered reliable. Itching and after-sensations in a short time became so disturbing that they often

prevented a certain discrimination between the real sensation and the associated dysesthesias. In these 4 persons one-half of the touch points were elicited with hairs of $\frac{1}{2}$ gm./mm.² the other half with hairs of 1 gm./mm.² over the forehead and cheek, while over the medial portion of the third division the ratio was 1 to 2, and over its lateral part 1 to 5.

These examinations suggest that the touch points of the face have no uniform threshold, but that the majority fall into two groups, one with electrical threshold of 1.5 ma and 15 volts and the other



FIGS. 1 to 4.—Frequency curves of rheobases of the first knocking sensation before and after subtotal retrogasserian neurectomy.

FIG. 1.—From the normal side of the face of a patient with trigeminal neuralgia.

FIG. 2.—From 10 normal persons.

FIG. 3.—From the pathologic side of the face of the same person as in Fig. 1 after subtotal retrogasserian neurectomy.

FIG. 4.—Postoperative mean values of 53 persons after subtotal retrogasserian neurectomy. Figs. 3 and 4 show the loss of the first peak of the frequency curve after subtotal section of the fifth nerve root.

with one of 3.5 ma and 40 volts. These findings are constant whether one examines a single division of the fifth nerve or the whole face, whether a single person or a group of persons. However, the two kinds of touch points are equally distributed only in the area of the first and second trigeminal divisions, whereas the number of points with higher threshold increases as we approach the outer part of the third division and the cervical segments.

From the data it appears that the higher values are more frequently found in the sensory areas where branches of cervical nerves

are likely to be most numerous while the lower values are largely confined to the trigeminal system. If this hypothesis should hold true, the frequency curves, after section of the fifth nerve, should lose their first peak. This is found to be the case. Figure 3 shows the postoperative frequency curve of the same patient whose pre-operative curve was given in Figure 1. Figure 1 represents the normal side. However, the abnormal side was not significantly different before operation. Figure 4 corresponds to Figure 2 and depicts the frequency of incidence of 53 postoperative threshold determinations in a number of patients. Both these curves plainly show that the maximum at 15v has disappeared while the maximum around 40v is still present.

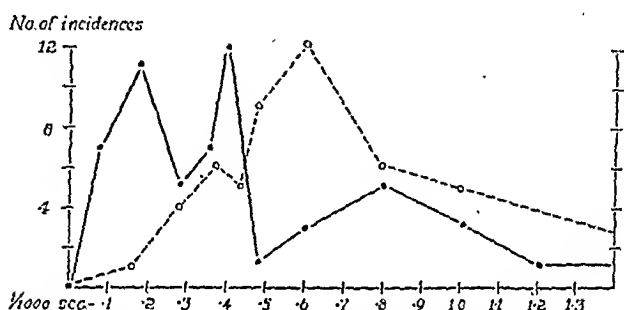


FIG. 5.—Frequency curves of the chronaxie of touch sensation before (—) and after (---) subtotal retrogasserian neurotomy. Loss of the first peak of the frequency curve after operation.

Accordingly, the touch points with a low mechanical threshold always disappear after subtotal section of the fifth nerve root, while those with a threshold of 1 gm./mm.² and more are present as a rule.

Briefly, there are *two sets of touch points in the face*, distributed in a definite mutual relation per square centimeter within the area of the three trigeminal divisions. One set has a mechanical irritability of $\frac{1}{2}$ gm./sq. mm. and a corresponding rheobase of 15v, the second has a threshold of 1 gm./sq. mm. and rheobase of 40v, central mean value, respectively. *After subtotal section of the fifth nerve root, the first group has more or less disappeared while the second remains unaltered.*

Turning from the mechanical and electrical threshold to the *time factor of touch sensation*, we find again the double peaked frequency curve (Fig. 5). The central mean of the two maxima is situated at 0.2 milliseconds and 0.4 milliseconds, respectively, in normal persons. After subtotal retrogasserian neurotomy, the figures at 0.2 milliseconds disappear, the values around 0.4 milliseconds remain and a new maximum appears at 0.6 milliseconds. This may mean a shift of the two maxima to the right. Or we may assume that those touch fibers which have escaped the section changed their chronaxie from 0.2 milliseconds to 0.6 milliseconds. One factor

definitely stands out, the maximum at 0.2 milliseconds has disappeared after root section as did the threshold values at 15v.

This is not so with *pain sensations*. The frequency curve of the time factor to a sharp sensation in normal persons has only one maximum. The central mean is found around 1.2 milliseconds in the distribution of the fifth nerve proper, and at 2.4 milliseconds in the lateral region of the third division where it borders on the cervical segments. After retrogasserian neurotomy these figures go up to 0.4 milliseconds and 0.8 milliseconds, respectively, at the points where pain sensations are preserved.

The greater uniformity of the irritability of the pain points in the normal face is also confirmed by their mechanical threshold. Thorns applied with $\frac{1}{4}$ gm. are adequate to stimulate 75% of all pain points in the areas of the first and second divisions of the trigeminal nerve and over the chin, 50% in the medial portion of the third division, and 20% in its lateral part. The remainder required $\frac{1}{2}$ gm.

The marked difference in the behavior of touch and pain sensation in the face following subtotal division of the trigeminal root is illustrated by the frequency of a total loss of each of the two sensations. Not more than 25% of our patients showed complete loss of touch sensation, but 77% loss of pain sensation in the second and third divisions. In other words:

1. In the region affected by the neurotomy, *painful sensations cannot be elicited in about three-fourths of the examined patients*, either mechanically or by currents of 25 ma and 250v. If a threshold exists, pain could not be produced unless electrical stimulation exceeded $\frac{1}{5}$ second duration.

2. *The frequency of a total loss of time excitability to a sharp sensation is 50% greater than to a knocking sensation.*

The clearest conception of the irritability of the sensory nerve fibers in the face in normal and neuralgic individuals as well as in persons after subtotal retrogasserian neurotomy, will be gained from surveying Table 1. The figures in this table indicate the *quantity of electricity in microcoulombs required to produce a touch or pain sensation*. The table shows that trigeminal neuralgia barely changes the irritability of the touch points while the irritability of the pain points is decreased in the most frequently attacked second and third division. The adjacent areas of the major auricular nerve are hyperalgesic. After subtotal root section a considerably greater stimulus is necessary to produce a touch and a pain sensation in the preserved sensory end organs. The fact that in this instance the larger electrode requires comparatively more current than the punctiform electrode—because of the smaller number of lines of force per sense organ—suggests that we are dealing with an absolute loss of pain points—penesthesia—in addition to an increase of threshold in those points where sensation is preserved—hypalgesia. Examination with graduated thorns confirm this assumption. An

alternate hypothesis to a change in threshold is that after operation only those points which originally had a high threshold retain their sensitivity.

TABLE 1.—THE QUANTITY OF ELECTRICITY IN MICROCOULOMBS REQUIRED TO PRODUCE A SENSATION.

	Diameter of electrodes, mm.	Touch.			Pain.		
		Normal side.	Neuralgic side.		Normal side.	Neuralgic side.	
			Preop.	Postop.		Preop.	Postop.
Forehead	1	3	2.4	19			
	1	16	16	16	30	30	160
	10	16	16	24	80	64	160
Cheek	1	3	3	53			
	1	16	19	28	48	72	280
	10	19	24	75	160	100	1850
3d division	1	3	3	24			
	1	16	16	16	48	96	160
	10	24	32	320	200	320	1600
Chin	1	3	4.2	27			
	1	16	24	16	38	48	320
	10	19	24	110	160	200	
Auric. mgn.	1	6					
	1	20	18	20	120	36	200
	10	40	39	82	200	100	1600

It has been explained above that after extirpation of the Gasserian ganglion a certain degree of tactile sensibility may be preserved. Conversely, we have examined patients in whom no sensitivity has returned for a longer period in the medial part of the face after a section of the fifth nerve root which was intended to be subtotal. The varying size of the completely anesthetic area seems to coincide with the extent of the beard free space. The assumption that tactile fibers from the lower part of the face, showing the functional characteristics of cervical filaments, may run over the fifth nerve is consistent with the anatomic facts.

I shall demonstrate elsewhere that the comparison of the healthy with the neuralgic side of the face in a patient with trigeminal neuralgia may occasionally show quantitative deficiencies in sensitivity, helpful in the problems of differential diagnosis. The small deviation from the normal in sensitivity over the neuralgic side of the face in a statistical treatment of the figures found in a large group of patients suggests, in my opinion, that a *quantitative change of sensibility*—implying a lesion of the trigeminal nerve and its ganglion—is a *contributory rather than an essential factor in the mechanism of neuralgia of the face*.

Summary. 1. The normal sensibility of the face was tested in 10 normal subjects and in 50 patients with unilateral trigeminal neuralgia. In the latter, tests were also made on the pathologic side both before and after subtotal section of the fifth nerve root. Five hundred and thirteen electrical determinations of threshold and 929 of excitation time both for touch and pain sensation were

treated with statistical methods. In addition, tests were made with graduated hairs and thorns.

2. Frequency curves, in which the threshold values of the touch points in volts are plotted against the number of incidences, show two maxima, the one at 15v, the other at 40v. After section of the fifth nerve root, the maximum at 15v disappears while the maximum at 40v remains unchanged.

3. Frequency curves of the time factor of touch sensations show a similar two-humped curve. The first of these two peaks disappears after section of the fifth nerve root.

4. The two sets of touch points are distributed in a definite mutual relation per square centimeter in the three areas supplied by the trigeminal divisions. Their ratios are 1:1 in those of first and second division; 1:2 in the medial area supplied by the third division, and 1:3 in the lateral part.

5. It is inferred from these observations that the touch points having a low mechanical and electrical threshold and a low time factor are innervated by the fifth nerve, those having high values are supplied by the cervical segments, while the pain points are supplied by the fifth nerve only.

6. The cervical segments overlap with their touch fibers the territory of the fifth nerve in the face with the exception of its most medial region.

7. The frequency curve of the time factor to painful stimuli has only one maximum. The majority if not all pain points within the area of the fifth nerve proper seem to be supplied by the fifth nerve. After retrogasserian neurotomy 75% of all patients suffer a complete loss of pain sensation, but only 25% a complete loss of touch sensibility.

8. In patients with trigeminal neuralgia the irritability of touch points over the neuralgic side of the face is not changed, the irritability of the pain points is slightly decreased. A quantitative change of sensibility in the face seems not to be an essential factor in the mechanism of neuralgia of the face. The peripheral nerve and its ganglion, therefore, are probably not the chief location of the lesion in trigeminal neuralgia.

9. The disturbance of sensibility after subtotal section of the fifth nerve root is characterized by a complete disappearance of some pain points—penalgesia. Those points that remain show a high threshold—hypalgesia. Either their threshold has been raised or only those points of abnormally high threshold have survived.

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PATHOLOGIC CONSIDERATIONS OF THE THORACIC DUCT.*

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THE thoracic duct has received comparatively little attention in the American literature. This, probably, is attributable to the rarity of conditions affecting it, its inaccessibility anatomically, and lack of interest in investigating its relation to disease in human beings. This study was undertaken to determine the incidence and type of conditions which affect it.

Methods of Study. The material on which this study is based was derived from 119 consecutive necropsies performed at The Mayo Clinic in 1937 and from reports of necropsies during the period 1929 to 1937. From the latter source, 3 cases of disease of the thoracic duct were selected because histologic sections or gross specimens were preserved and available for examination.

The thoracic duct was approached from the thoracic aspect of the structure above the diaphragm. It was isolated, followed downward from the thorax, the cisterna chyli identified when possible, and the principal trunks emptying into the duct were dissected free. Any closely adherent lymph nodes were dissected out together with the trunks and cisterna chyli and were included in the structures removed. In most cases, it was impossible to follow the duct through the thorax and neck to the junction with the venous angle owing to limitation of the necropsy incision in the neck. It was followed as far cephalad as possible and was removed as a whole. Injection of the duct was not carried out owing to the delicacy of the wall in fresh tissue, and because injection would force out any material such as carcinomatous cells, blood, or other cellular structures which would be of interest in a study of this type. In most cases, as much as possible of the surrounding fibrous and adipose tissue was included in the dissection in order to make larger blocks for imbedding and cutting, and to include interesting lymph nodes or inflammatory tissue in the periductal structures.

After removal, the duct was placed in 10% formalin for 24 hours before blocks were cut for histologic sections. Representative cross-sections were cut from various levels, of the cisterna chyli and thoracic duct, imbedded in paraffin, cut, and stained with hematoxylin and eosin. Gram stains of the tissues were made when indicated.

Report of Cases and Findings at Necropsy. The following 12 cases were found in which there was involvement of the thoracic duct by a pathologic process. In Cases 1, 2, and 3, suppuration of the

* Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M.S. in Medicine.

thoracic duct and cisterna chyli were discovered at necropsy. In Cases 4, 5, 6, 7, and 8, carcinoma was found involving the cisterna chyli or thoracic duct. In Cases 9, 10, and 11, thrombosis of blood was found in the duct, and in Case 12, perilymphangitis of the thoracic portion of the duct was found.

CASE 1. The patient was a white man, aged 30. The chief complaints were diarrhea, occasionally bloody, for 1 year; loss of weight and strength during the last 6 months; nocturnal edema of the ankles for the past 3 or 4 weeks. Examination at home revealed diffuse polyposis of the colon. Examination at the clinic confirmed this diagnosis and roentgenologic examination revealed a filling defect suggestive of carcinoma in the descending portion of the colon. There were cardiac findings suggestive of bacterial endocarditis and repeated blood cultures revealed hemolytic streptococci. The patient's course in the hospital was marked by a septic type of fever, a stuporous and irrational mental condition, and a steadily downhill course. Death occurred on the 17th day after admission.

Findings at Necropsy. At necropsy, the significant findings were polyposis of the colon with carcinomatous change, ulcerative vegetative endocarditis of the mitral and aortic valves, acute diffuse nephritis, multiple infarcts of the spleen and kidneys, multiple abscesses of the cardiac muscle, multiple infarcts and abscesses of the brain, infarcts of the lungs, and multiple abscesses of the periaortic lymph nodes. The thoracic duct and cisterna chyli were markedly dilated, reddish-yellow in color, and surrounded by large, red, soft lymph nodes. The cisterna measured 2.5 cm. in diameter. The thoracic duct varied in diameter throughout its course, ranging from 1 to 0.5 cm. The duct entered the left subclavian vein at the junction of that vein with the left internal jugular. On cutting through the cisterna after fixation in formalin for 24 hours, a yellowish-pink material, semiliquid in consistency, coiled out. There were several enlarged lymph nodes adherent to the cisterna and its large trunks. Histologic sections of the cisterna revealed the following: the walls were infiltrated with neutrophils and there was marked degeneration and narrowing of the muscularis. The endothelial lining was indistinct. The lumen was occupied by a mass of fibrin, leukocytes, and endothelial cells. At one point, the thrombus and wall of the cisterna chyli were intimately associated by means of fresh fibrous connective tissue. There was marked leukocytic infiltration of the surrounding connective tissue. A lymph node adjacent to the cisterna contained several nodules of metastatic carcinomatous cells. The lymphoid tissue of the nodes was hyperplastic. Sections made through the cervical portion of the thoracic duct revealed the same picture of thrombosis and suppuration. Gram stains of the sections disclosed Gram-positive cocci in short chains resembling streptococci (Fig. 1).

This patient died of sepsis incident upon bacterial endocarditis with multiple infarction of almost every organ in his body. In addition, he had polyposis of the colon with carcinomatous change in several regions which probably antedated the bacterial endocarditis. There were abscesses in the periaortic nodes and these nodes drain directly into the radicles of the cisterna chyli; it is possible that the source of infection in the thoracic duct was the abscessed nodes. The lymphatics of the colon drain to the mesenteric and, thence, to the periaortic or lumbar nodes. Ulceration and formation of abscess in polyps or carcinomas of the colon are not uncommon and this condition might have served as the original focus of infection

leading to suppuration in the thoracic duct. From the duct, the organisms pass readily into the blood stream and it is probable that this was the route of infection leading to vegetations on the valves of the heart.

CASE 2. The patient was a white man, aged 59. The chief complaints were pyrosis and eructation for 5 years, cramping pain across the upper abdomen for 2 years, and fever, night sweats, nausea, vomiting, and pain in the umbilical region for the past 3 weeks. Examination revealed moderate emaciation, jaundice, and enlargement of the liver. Laboratory studies disclosed sugar in the urine, elevation of the serum bilirubin, and a non-functioning gall bladder was discovered by cholecystography. He was admitted to the hospital at once and his course there was marked by severe chills and fever, progressive elevation of the blood urea, a decreasing urinary output, and, terminally, cyanosis and coma. Death occurred before surgical relief could be attempted.

Necropsy. Necropsy revealed carcinoma of the head of the pancreas with necrosis and formation of abscess. There was a fistulous communication between the pancreas and duodenum and between the pancreas and common bile duct, multiple abscesses of the periaortic lymph nodes and thoracic duct, and marked bilateral pyelonephritis. The wall of the cisterna chyli and lower portion of the thoracic duct was necrotic. Histologic sections of the cisterna and duct revealed marked necrosis of the wall, infiltration of the surrounding tissues by neutrophils, and the endothelial lining of the duct was replaced by masses of bacteria which stained deep blue with hematoxylin.

The source of infection, in this case, was an abscess and necrosis of the pancreas with involvement of the periaortic lymph nodes. These nodes, in turn, led to infection of the thoracic duct. Blood cultures were not taken, but it is likely that they would have been positive because the thoracic duct was not occluded and organisms had ready access to the general circulation.

CASE 3. The patient was a white man, aged 51. The chief complaints were epigastric pain and distress after meals for 35 years. These symptoms began after the swallowing of lye. They were relieved by soda or milk. The last episode of distress began 3 weeks before admission to the clinic and was not relieved by alkali or milk. Examination revealed moderate epigastric tenderness and marked anemia. Surgical exploration after preparation of the patient disclosed a subacute perforating ulcer in the pylorus for which posterior gastro-enterostomy was performed. The postoperative course was stormy, marked by bilateral bronchopneumonia and pleural effusion. There was progressive failure and death occurred on the 10th postoperative day.

Necropsy. At necropsy, there was found edema of the lungs and bronchopneumonia. The only other finding of significance was chronic suppuration of the thoracic duct and cisterna chyli. There was a small abscess in one of the periaortic lymph nodes. There was pus in the cisterna, in its large branches, and in the thoracic duct throughout its course. The tissue surrounding the duct was indurated and there was evidence of inflammation. Histologic examination of the thoracic duct revealed necrosis and leukocytic infiltration of the wall of the organ and the lumen was filled with neutrophils. The surrounding areolar tissue also was infiltrated with leukocytes (Fig. 2).

In this case, as well as in the 2 previously reported, suppuration of the cisterna chyli and thoracic duct was associated with forma-

tion of abscess in the periaortic lymph nodes which drain directly into the cisterna chyli by way of the large lymphatic trunks. It is likely that, in this case, infection followed surgical operation and led to formation of abscess in the periaortic node. From the abscess in the node, infection spread through the lymphatic trunks to the cisterna chyli and thoracic duct and from the general circulation affected the lungs, thus leading to pneumonia.

CASE 4. The patient was a white woman, aged 65. The chief complaint was of a tender nodule in the right breast with redness of the overlying skin, first noticed 10 months previously. Seven months previous to coming to the clinic, intensive deep Roentgen therapy was given. Cough developed during the course of these treatments, but disappeared in 2 months. For the preceding 3 months a small, painful mass had been present over the right second costosternal junction. Examination revealed dimpling and slight retraction of the nipple of the right breast and there was a firm mass 3 by 5 cm. in extent beneath the skin in the upper outer quadrant. The right axillary nodes were enlarged and there was a tender mass near the right second costosternal junction. Roentgenologic examination of the chest disclosed old fibrous tuberculosis with cavitation in the right upper lobe with extension to the right lower lobe. There was no metastasis evident in the thorax. Radical amputation of the right breast was performed. On the 14th postoperative day cough and dyspnea developed. Roentgenologic examination of the thorax at the bedside gave evidence of fluid on the right side and evidence of carcinomatous metastasis in the right hilus. Aspiration of fluid from the right pleural cavity controlled the effusion. The fluid was brown in color, cultures were negative, and cytologic examination revealed no carcinomatous cells. The patient gradually failed and there was increasing dyspnea and elevation of the pulse rate. Death occurred 53 days after operation.

Necropsy. At necropsy there was found hemothorax on the right side, acute seropurulent pericarditis, residual carcinoma in the anterior part of the mediastinum and in the first and second ribs on the right, in the left axillary nodes and hilus of the right lung. The cisterna chyli and thoracic duct appeared normal grossly, but the surrounding connective tissue in the thoracic portion was indurated and hemorrhagic. Sections through the thoracic portion of the duct revealed carcinomatous cells invading the wall and appearing as nests of cells in the muscularis (Fig. 3).

This patient gave evidence of extensive carcinoma of the mediastinal structures secondary to carcinoma of the breast. The malignant process had spread through the pleura to invade the retropleural tissues and the thoracic duct was involved by direct extension.

CASE 5. The patient was a white man, aged 77. The chief complaints were recurrent epigastric distress 1 to 2 hours postprandially, occurring at intervals for the past 20 years. For 5 months there had been progressive anorexia and loss of 45 pounds. For the past 3 weeks vomiting of coffee-ground material after meals had occurred. Examination revealed a palpable mass in the right upper quadrant of the abdomen below an enlarged liver. Roentgenologic examination of the stomach disclosed an obstructing lesion at the outlet of the stomach. On surgical exploration this mass was found to be an inoperable carcinoma situated at the pyloric end of the stomach and had perforated into the pancreas and liver. On the 5th day, postoperatively, there appeared signs of bronchopneumonia. His condition became progressively worse and death occurred on the 6th postoperative day.

Necropsy. At necropsy there was found carcinoma of the gall bladder with obstruction of the pylorus, invasion of the liver, and metastasis to the liver, regional lymph nodes, and hepatic flexure of the colon. There was extensive bronchopneumonia and beginning empyema. The thoracic duct and cisterna chyli were not grossly affected, but histologic examination of the cisterna chyli and abdominal portion of the thoracic duct revealed carcinomatous cells invading the wall of the cisterna and replacing the endothelial lining of that vessel. There were masses of carcinomatous cells in the lumen of the cisterna not attached to the wall.

CASE 6. The patient was a white man, aged 64. On admission to the clinic the diagnosis of carcinoma of the stomach was made. His condition was very poor and he was hospitalized at once. Before any examinations could be carried out he went into shock and died suddenly.

Necropsy. At necropsy there was found carcinoma of the stomach with metastasis to the liver, periaortic lymph nodes, and nodes surrounding the cisterna chyli. No cause was found for his sudden collapse and death. The thoracic duct was completely obstructed by the enlarged lymph nodes compressing it and there was 1000 cc. of chylous fluid in the peritoneal cavity. Histologic examination of the cisterna chyli and thoracic duct revealed no invasion of these vessels, but one of the large trunks adjacent to a carcinomatous lymph node was infiltrated by carcinoma which had replaced the endothelium.

In the last 2 cases, carcinoma had invaded the lymphatic vessels and had formed an epithelial lining of high columnar cells replacing the normal flat endothelium. In addition, the abdominal portion of the duct and the cisterna were encroached upon to the extent that the flow of lymph was obstructed and chylous ascites developed.

CASE 7. The patient was a white man, aged 64. The chief complaints were loss of weight, pain in the epigastrium, and vomiting of the obstructive type. Examination disclosed marked emaciation and enlargement of the liver. Roentgenologic examination of the stomach gave evidence of an obstructing lesion at the pylorus. At surgical exploration, there was found carcinoma of the pylorus with metastasis to the liver and regional lymph nodes. The patient died suddenly on the 2d postoperative day, of pulmonary embolism.

Necropsy. At necropsy, the diagnosis of pulmonary embolism was confirmed; the iliac veins were thrombosed and, apparently, served as the source of embolism. There was extensive carcinoma of the pylorus with

LEGENDS FOR FIGS. 1, 2, 3 AND 4.

FIG. 1.—(Case 1.) The wall of the thoracic duct in the upper mediastinum is infiltrated with leukocytes and the lumen is occupied by a thrombus of fibrin and leukocytes. Brown Gram stains reveal Gram-positive cocci in chains in the thrombus. There is considerable reaction in the periductal tissues, manifested by leukocytic infiltration. (× 21.)

FIG. 2.—(Case 3.) The wall of the thoracic duct is markedly thickened by replacement of muscle by fibrous tissue and there is neutrophilic infiltration of the wall. The lumen is occupied by a canalized thrombus consisting of necrotic debris, fibrin, leukocytes and bacteria. The periductal connective tissue shares in the chronic inflammatory process. (× 25.)

FIG. 3.—(Case 4.) A large lymphatic trunk adjacent to the cisterna chyli shows carcinomatous invasion of its wall. The carcinomatous cells stain deeply and stand out from the surrounding muscular tissue. (× 85.)

FIG. 4.—(Case 10.) This section was taken from the thoracic duct in the upper mediastinum and shows the thoracic duct occupied by a fresh thrombus similar to that seen in the cisterna chyli in Fig. 2. The lymph node adjacent to the duct shows Hodgkin's disease. (× 24.)



FIG. 1



FIG. 2



FIG. 3

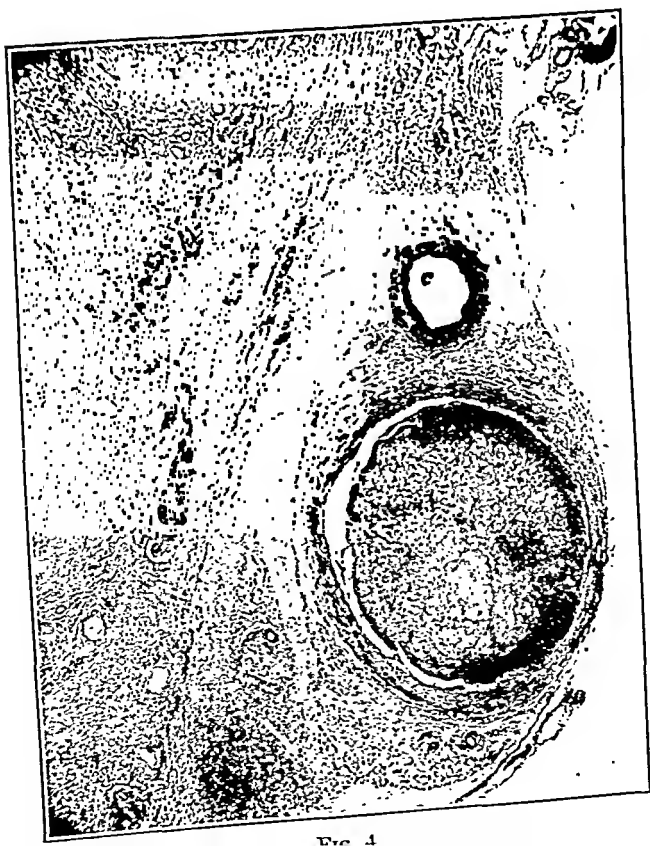


FIG. 4

metastasis to the regional lymph nodes, liver, and thoracic duct. There was extensive infiltration of the periductal tissues also, but no sign of obstruction was present. Histologic examination of the duct disclosed infiltration of the wall with carcinoma and almost complete obliteration of the lumen.

This patient, in spite of marked obstruction of the lumen both from within and without, had no signs of lymphatic stasis. It is likely that there was adequate collateral circulation of lymph and anomalous connections with the venous system so that chylous effusion was prevented.

CASE 8. The patient was a white woman, aged 68. The chief complaints were of recurrent attacks of severe right upper quadrant pain projected toward the intrascapular region, jaundice for the past 2 weeks, and fever at high as 102° F. (38.8° C.). Examination revealed mild icterus and a palpable mass in the right upper quadrant of the abdomen. Roentgenologic examination gave negative results except for elevation of the right leaf of the diaphragm. At surgical exploration, there was found metastatic carcinoma of the liver and multiple calculi in the gall bladder. The patient did well until the 12th postoperative day when signs of fluid were discovered in both pleural cavities. Despite repeated aspiration of the fluid there was steady failure and death occurred on the 31st postoperative day.

Necropsy. Necropsy revealed carcinoma of the tail of the pancreas with metastasis to the liver, lungs, diaphragm, lymph nodes, and heart. There was a thrombus composed of a mass of tumor in the hepatic vein. The gall bladder was chronically infected and filled with calculi. The cisterna chyli and thoracic duct were grossly normal, but histologic examination of the cisterna revealed a minute collection of carcinomatous cells in the lumen. The walls of the cisterna were not affected by the malignant process.

In this case the only carcinoma found in the thoracic duct was a small embolus in the lumen. It is possible that carcinoma may be disseminated in this way to reach the heart and lungs, although, in this case, carcinoma in the hepatic vein appeared to be the more likely explanation of spread from the abdominal cavity.

CASE 9. The patient was a white man, aged 44. The chief complaints were vague abdominal distress for the past 25 years, an episode of marked weakness diagnosed as anemia 5 weeks before admission to the clinic, followed in a few days by severe pain in the right lower quadrant of the abdomen, severe diarrhea for the past 2 weeks, accompanied by the passage of dark blood, and fever daily for the past 2 weeks. Examination disclosed a firm, nodular mass in the right lower quadrant of the abdomen. Roentgenologic examination gave evidence of signs of ulcerative ileitis with a granulomatous formation and the presence of a large mass extrinsic to the cecum. At surgical exploration, the terminal ileum, ascending colon, and part of the transverse colon were resected for ulcerated, annular, perforated carcinoma of the cecum with involvement of the regional lymph nodes and right ureter. The postoperative course was remarkably good for 8 days when jejunostomy had to be performed because of ileus. The following day, intermittent hemorrhages from the large bowel began and death occurred on the 11th day postoperatively.

Necropsy. At necropsy, there was found retroperitoneal hemorrhage, resolving fibrinous peritonitis, and right hydronephrosis. The cisterna chyli and thoracic duct appeared normal, grossly. Histologic examination of sections taken through the cisterna revealed a large, fresh thrombus with lymphocytes scattered about occupying the lumen of the cisterna.

Why blood should occupy the cisterna and thoracic duct is difficult to explain by anatomic dissection. It may be that retroperitoneal hemorrhage with effusion of blood into the lymph spaces and vessels causes a flow of blood through normal lymph-bearing trunks into the cisterna where thrombosis occurs.

CASE 10. The patient was a white man, aged 25. The chief complaints were of chills and fever intermittently for the past 3 months. In the past 2 years, he had experienced pneumonia and empyema and, 7 months before admission to the clinic, he had "flu" and diarrhea for 2 weeks. Four months previously, he had pneumonia from which he recovered in 2 or 3 weeks, but shortly thereafter chills and fever occurred and had persisted. Examination revealed marked emaciation and pallor. There was a harsh systolic murmur over the base of the heart. The spleen was markedly enlarged. The concentration of hemoglobin was 4.5 gm. per 100 cc. of blood. The erythrocytes numbered 2,000,000 and the leukocytes 1200 per c.mm. The percentages of various types of leukocytes were as follows: lymphocytes 58, monocytes 2.5, and neutrophils 39.5. There were few signs of toxicity in the neutrophils, no immaturity, and good regeneration of erythrocytes. Repeated studies of the blood showed reticulo-endothelial cells on one occasion. The monocytes varied from 2 to 30%, and the total number of leukocytes from 1200 to 7400 per c.mm. Repeated blood cultures were negative, as were agglutination tests for typhoid, paratyphoid, Brucella, and tulareuse. Examinations of the sputum revealed no acid-fast bacilli. During his course in the hospital the patient's temperature ranged from 101 to 104° F. (38.3 to 40° C.), with a corresponding variation in the pulse rate. Blood transfusions and sulphanilamide were given. Five days before death, severe jaundice began and progressed in degree. Death occurred on the 19th day after admission to the hospital.

Necropsy. The spleen was found to be markedly enlarged, the weight being 1700 gm. There was focal necrosis in the spleen, liver, and lymph nodes of the mediastinum and abdomen. There was effusion of fluid into all the serous cavities. The thoracic duct was slightly dilated, but the cisterna chyli was markedly enlarged, bluish-red in color, and was filled with material of liquid consistency. The diameter of the cisterna chyli was 1.5 cm. and the trunks emptying into it were dilated to approximately four times their normal size. The duct, cisterna, and large branches were ligated and removed. Histologic sections revealed the cisterna filled by a large thrombus of fibrin, erythrocytes, and lymphocytes. The trunks were also filled with blood. The walls were thinned but no abnormality, such as leukocytic or lymphocytic infiltration, was seen. The adjacent lymph nodes revealed Hodgkin's disease (Fig. 4).

In this case, as in Case 9, there was thrombosis of blood in channels which normally carry lymph. There was no retroperitoneal hemorrhage to account for effusion of blood into lymph spaces and channels and no satisfactory explanation is forthcoming to account for it. Enlargement of the liver, spleen, lymph nodes, or any mass in the abdomen which compresses the venous channels could raise venous pressure locally and give rise to a reflux of blood into lymphatics through fortuitous lymphaticovenous communications.

CASE 11. The patient was a white man, aged 61. The chief complaints were loss of weight during the past 4 months, recurring epigastric distress relieved by alkali and food for the past 3 years, pain in the epigastrium

referred into the back, and vomiting of digested blood for the past 3 weeks. Examination at the clinic revealed marked emaciation and weakness. Roentgenologic examination of the stomach disclosed ulcerating carcinoma of the middle third. On gastric analysis, free hydrochloric acid was 36 and the total acidity was 76. The concentration of hemoglobin was 5.04 gm. per 100 cc. of blood and the erythrocytes numbered 2,000,000. At surgical exploration, partial gastrectomy for carcinoma of the middle third of the stomach was carried out. A posterior Polya type of anastomosis was made. Partial resection of the transverse mesocolon was necessary because of extension of the neoplastic process. On the 1st postoperative day the patient suddenly went into shock and died before supportive measures could be attempted.

Necropsy. Necropsy revealed hypertrophy of the heart with dilatation of the left ventricle. No residual carcinoma was found. The thoracic duct and cisterna chyli were grossly negative, but histologic examination of stained sections revealed a recent, trabeculated thrombus containing fibrin, erythrocytes, and lymphocytes occupying the lumen of the cisterna chyli.

In this case, shock with a rise of venous pressure occurred before death. There was a recent thrombus in the cisterna chyli. It is probable that a reflux of blood through lymphaticovenous communications along the course of the thoracic duct resulted in the appearance of blood in the cisterna chyli. Injury to the cisterna in the course of a surgical operation is not a likely possibility, as it is protected well by the muscles of the diaphragm where they originate over the lumbar vertebræ. However, trauma to lymph nodes in the mesentery and periaortic region may give rise to hemorrhage, and blood may appear in the lymphatic trunks which empty into the cisterna. In this case, either the first or third explanation offered is possible to account for blood in the cisterna chyli.

CASE 12. The patient was a white man, aged 61. The chief complaints were a cough with production of much sputum for the past 4 years, fetid breath for 4 years, and marked loss of weight. In 1932, the patient had "flu" followed by thoracic pain, cough, and purulent sputum. A diagnosis was made, elsewhere, of pulmonary abscess. Three years before, he had experienced a pulmonary infection followed by hemoptysis and an increase in the amount of sputum. Phrenicectomy was carried out elsewhere. For the past 3 years there had been persistent, copious production of sputum and frequent hemoptysis. Loss of 52 pounds occurred during the past 4 years. Examination at the clinic revealed emaciation and fetid breath. There was transient auricular fibrillation, the fingers and toes were clubbed, and roentgenoscopic examination of the thorax revealed old fibroid lesions of the left apex and almost complete obliteration of the remainder of the lung by multiple large cavities. Bronchoscopy disclosed a deformity of the left main bronchus and purulent material filling the bronchus. A biopsy of the wall of the bronchus gave evidence of inflammatory material. The subsequent course was steadily downhill with fever and marked prostration. He died 7 days after bronchoscopic examination.

Necropsy. Necropsy revealed bronchiectasis with multiple abscesses in the left lung. There was hemorrhage into the bronchial cavities and organized pneumonia in the right lower lobe. The gall bladder contained multiple calculi and the wall was chronically inflamed. The thoracic duct above the diaphragm was surrounded by inflammatory tissue. Histologic examination of sections of the duct taken from this region showed lymphocytic infiltration of the periductal tissue and organization of inflammatory

tissue in the region. The muscularis of the wall of the duct did not stain well and the lymphatic vessels of the periductal tissue were filled with leukocytes and red blood cells.

In this case there was perilymphangitis of the thoracic duct. The wall of the duct was affected and, had the process been more acute, suppuration and necrosis might have taken place. No evidence of tuberculosis was found in this patient.

Summary. The thoracic duct has been examined in 119 consecutive autopsies. In this group, 8 cases were encountered in which the thoracic duct was involved in disease processes, namely, 1 case of suppuration, 1 of perilymphangitis, 4 of carcinomatous involvement, and 2 of thrombosis. In addition, 2 cases of suppuration and 2 of carcinomatous involvement were reported from necropsies performed previous to this study. In the series of 119 cases there were 43 different conditions found to be the primary cause of death. In none of 19 cases of peritonitis were there signs of inflammation or suppuration in the thoracic duct. Of 50 cases of carcinoma in this series 4 were associated with carcinomatous involvement of the thoracic duct.

In this small series, carcinoma and suppurative conditions were found to be the commonest conditions affecting the thoracic duct. There were only 2 cases of tuberculosis encountered in the series and neither of these gave evidence of involvement of the thoracic duct. It has been usually found that tuberculosis ranks second to carcinoma; the difference is probably due to the special type of cases met in this clinic.

Suppuration in the thoracic duct is rare and it is significant that, in the 3 cases reported in this study, all were secondary to suppuration in the periaortic lymph nodes. The presence of blood in the thoracic duct was encountered in many more cases than the 3 presented in the case reports. It is not uncommon to find blood in the sinuses of lymph nodes. Anatomically, it is easy to conceive of its passing from the lymph sinuses to the large trunks emptying into the cisterna chyli and thoracic duct. However, from the physiologic standpoint, this process would require a considerably higher venous pressure than usually obtains. It may be that this is an agonal process occurring shortly before death in the majority of cases. In the cases of thrombosis reported, the clots were well formed and, in one, the cisterna was greatly dilated, indicating that blood had been present for a longer period than could be accounted for by an agonal process.

The relation of the thoracic duct to the pathogenesis of disease conditions in the body has been considered in the comments given after the case reports. Were the cisterna chyli and thoracic duct examined routinely at necropsy in large series of cases, interesting conclusions might be drawn as to the spread of disease from one part of the body to another through channels other than those carrying blood.

BOOK REVIEWS AND NOTICES.

HANDBOOK ON SOCIAL HYGIENE. Edited by W. BAYARD LONG, M.D., Attending Dermatologist and Director of Dermatology and Syphilis Clinics in St. Luke's Hospital, New York, etc., and JACOB A. GOLDBERG, M.A., PH.D., F.A.P.H.A., Secretary, Social Hygiene Committee, New York Tuberculosis and Health Association, and Social Hygiene Council of Greater New York. With a Foreword by EDWARD L. KEYES, M.D., Professor Emeritus of Clinical Surgery (Urology) in Cornell University Medical College, New York. Pp. 442; 62 illustrations. Philadelphia: Lea & Febiger, 1938. Price, \$4.00.

THE editors and 17 contributors have made a valiant effort to supply medical and interested lay people with a handbook on social hygiene. When one realizes the diversified audience aimed at, this book can be looked upon as more than a pioneering effort. It is truly a handbook covering every phase of the subject. Nowhere else, to the Reviewer's knowledge, is available an authoritative up-to-date compilation in so brief a compass of the data on social hygiene such as is here produced. Furthermore, in spite of the many contributors, a uniform style of presentation and unanimity of opinion on controversial subjects has been attained. Clarity and full understanding of the subject matter is assured for the casual reader by excellent concise summaries at the end of most chapters; the more enquiring reader is supplied with a rather complete bibliography at the end of each chapter. Thus, in a small book of some 400 pages, the editors have produced a compendium which is both informative and provocative of further study in the important and ever-dynamic subject of social hygiene.

With no desire to find fault, certain criticisms regarding important omissions or non-conventional points of view expressed in this work must be pointed out. Outstanding among the omissions are: summary of the facts of infectiousness, especially of syphilis; discussion of relapse or recurrence in syphilis; a specific week-by-week schedule, such as that of the Coöperative Clinical Group, for the treatment of early syphilis; and syphilophobia. It is a little distressing to a modern syphilologist still to have toilet seat infections or abortive cure of syphilis, mentioned without a condemnatory note. Syphilis is conceded to be systemic from the start, yet on page 43 one reads about secondary syphilis: "The eruption signifies that the spirochetes have gained entrance to the blood stream and have been carried to all tissues and organs of the body." Latent syphilis seems to be regarded as to some extent synonymous with late syphilis, since, after a careful statement of the necessity for complete study of a latent syphilitic patient before treatment is instituted, one of the collaborators goes on to discuss how treatment should be modified if cardiovascular or kidney complications are discovered in latent syphilitics.

While the first visit to a clinic is rated so important in case holding that "the majority of patients require no additional follow-up work," no detailed account is given anywhere in this book of the content of the first interview with the patient. Furthermore, follow-up by mail which is advocated in this handbook, does not in our experience compare at all favorably with personal follow-up methods.

If one ignores such occasional deviations or omissions, this work deserves the attention of physicians, nurses and social workers. It should not, however, be used by physicians as a substitute for more extended works on syphilis and gonorrhea.

H. B.

CUTANEOUS CANCER AND PRE-CANCER. A Practical Monograph. By GEORGE M. MACKEE, M.D., Professor of Clinical Dermatology and Syphilology and Director of Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital, Columbia University; and ANTHONY C. CIPOLLARO, M.D., Associate in Dermatology, Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital, Columbia University. With a Foreword by FRANCIS CARTER WOOD, M.D. Pp. 222; 231 illustrations. New York: The American Journal of Cancer, 1937. Price, \$3.75.

THIS practical little volume discusses the symptomatology, diagnosis, etiology, pathology and treatment of cancer of the skin and the precancerous dermatosis. There are 231 excellent illustrations. The photomicrographs are exceedingly fine. There are four general sections and a good index. A wide variety of precancerous lesions are discussed as well as the carcinomas and sarcomas of the skin. The lymphoblastomas are briefly reviewed, although the authors acknowledge that "strictly speaking they do not belong in the group of carcinomas and sarcomas." Each section is followed by an adequate and well-selected bibliography. The monograph is not intended as a reference book, but as a manual of undisputed facts. This work will receive wide recognition from general practitioners and surgeons as well as from the author's colleagues in dermatology as it should.

I. R.

METHODS OF TISSUE CULTURE. By RAYMOND C. PARKER, PH.D., Associate in Experimental Surgery, The Rockefeller Institute for Medical Research, New York. With a Foreword by ALEXIS CARREL, M.D. Pp. 292; 109 illustrations. New York: Paul B. Hoeber, Inc., 1938. Price, \$5.00.

THIS book gives the essential details of the basic techniques developed in Carrel's laboratory. Many new and highly original methods are described which have not before been published, *e. g.*, Colonel Lindbergh's method for separating serum from plasma; others are modifications of techniques described in former articles.

The author's discussion of the main techniques involved in tissue culture work is so detailed and clear that from his descriptions and illustrations a beginner could certainly obtain a fairly comprehensive knowledge of the subject. He weighs one method of culturing different types of tissue against another, points out possible sources of error, recommends workable solutions, and on the whole clarifies the most essential problems to be encountered.

The greater part of the manual concerns itself with technical details which are necessary for the success of the tissue culture technique.

The Carrel flask culture method is fully described and highly recommended for growing all types of tissue. This method affords a relatively stable system in which both the effect of the cells on the medium and the effect of the medium on the cells can be studied simultaneously. The pH of the medium can easily be adjusted by Carrel's technique of gas control. The author prefers the flask method since it is applicable to more types of experiments and various tissue than any other method.

Tissue culture work on tumors has revealed a wealth of information concerning the nature of the cells themselves, their malignancy, and how they differ from normal tissue. One of the most important problems which first confronted investigators was whether the tumor cells retained their malignancy *in vitro*. As a result of experiments performed by Rous, Lewis, Carrel, and others, it has been proven that the malignancy of tumor cells is not lost even after innumerable transplantations or many passages through animals. Just as normal cells retain certain specific functional

properties when cultivated *in vitro*, so tumor cells retain their malignancy which "is a permanent characteristic located in the cell itself."

Most of the experiments on the propagation of viruses using tissue culture techniques have been done very recently. In this book the author reviews the most important work which has been done and is still being done in this field. Among such experiments are those on the species specificity of viruses, the propagation of viruses with living tissues without loss of virulence, and the vaccination of animals with virus material which has been developed not in animals, but in conjunction with tissue fragments in culture.

In summary, the author has analyzed the most important phases of tissue culture techniques and has presented clearly the most recent procedure and developments in the field.

B. L.

THORACIC SURGERY. A Revised and Abridged Edition of Sauerbruch's "Die Chirurgie der Brustorgane." By FERDINAND SAUERBRUCH, Professor of Surgery in the University of Berlin; and LAURENCE O'SHAUGHNESSY, F.R.C.S., Hunterian Professor in the Royal College of Surgeons of England; Consulting and Thoracic Surgeon to the British Legion Sanatorium, Preston Hall, and to the Nottinghamshire County Council, etc. Pp. 394; 215 illustrations and 15 colored plates. Baltimore: William Wood & Co., 1937. Price, \$13.50.

THIS revised and abridged edition of Sauerbruch's "Die Chirurgie der Brustorgane," which was published in 1918, and again in 1921, 1924, 1928 and 1930, will be most welcome. O'Shaughnessy has, in his translation and abridgment, accomplished something for which surgeons in the English-speaking world will remain in his debt. It is a volume which can be read with profit not only by the thoracic surgeon, but by general surgeon, internist and tuberculosis specialist. There are 17 chapters, a bibliography and an author and subject index. Lesions of the chest wall are reviewed as well as lesions of the pleura, lungs, heart and pericardium, mediastinum, esophagus and diaphragm. There is a separate chapter on the "Surgical Treatment of Cardiac Ischemia." The paper, type, composition and illustrations are excellent. Although in many minor points there may be some disagreement in methods of treatment, or in special techniques, the volume offers the opinion of one of the peers in the field of thoracic surgery. As such it will be widely received. No one interested in the surgical problems of the thorax can afford to be without it.

I. R.

THERAPIE DER TUBERKULOSE. VOLS. 1 and 2. Herausgegeben von PROF. DR. J. BERBERICH, Frankfurt, und Dozent DR. P. SPIRO, Davos. Pp. 845; illustrated, 1 colored plate. Leiden: A. W. Sijthoff's Uitgever-smaatschappij, N. V., 1937. Price, Paper, Hfl. 25.00; Bound, Hfl. 28.50.

In this work methods of therapy are based on present-day knowledge of the pathology, bacteriology, immunology and pathogenesis of tuberculosis. Authors are a distinguished group of investigators and clinicians predominantly continental, but including several workers now in England and America.

The first volume opens with a historical review of therapeutic concepts since Laennec. There follow chapters giving detailed consideration to bacteriologic and immunologic methods and theories. The chapters on the pathology of tuberculosis emphasize the changes that occur in response to various therapeutic measures. The diagnostic uses of tuberculin and Roentgen ray are concisely discussed. The volume is concluded by chap-

ters on tuberculin therapy, vaccination, chemotherapy, and occupational therapy.

In the second volume treatment is described system by system, including the upper respiratory tract, lungs, circulatory system, gastro-intestinal tract, reticulo-endothelial system, bones and joints, genito-urinary tract, skin, eye, ear and nervous system. In the chapters on pulmonary tuberculosis, rest treatment, the rôle of diet, climate and physiotherapy are discussed as well as symptomatic management. Collapse therapy and surgical procedures are more elaborately considered. Also of particular interest to the surgeon is the section on bone and joint tuberculosis, which includes admirably concise but detailed descriptions of operative methods. Chapters are devoted to the treatment of tuberculosis in children and in the aged, in diabetes and in the pregnant. Finally, there is a chapter on psychotherapy.

It is obvious that this work covers a wide field in considerable detail. There is some unavoidable repetition, but the inclusion of this wealth of material within two volumes is a tribute to the skill of the authors. There is an adequate index, and the contributors have in most instances appended extensive bibliographies. These volumes should be especially useful as a work of reference in any problem of treatment.

H. H.

 SYPHILIS, GONORRHEA AND THE PUBLIC HEALTH. By NELS A. NELSON, B.S., M.D., F.A.P.H.A., Director, Division of Genitoinfectious Diseases, The Massachusetts Department of Public Health; and GLADYS L. CRAIN, R.N., Epidemiologist, Division of Genitoinfectious Diseases, The Massachusetts Department of Public Health. Pp. 359; illustrated. New York: The Macmillan Company, 1938. Price, \$3.00.

THE authors have endeavored to bring together, in condensed form and under one cover, the much diversified knowledge pertaining to the public health aspects of genito-infectious disease control. The work should be read not only by physicians interested in the rapidly developing national public health movement and social work courses in this field, also by health officers and public health workers in general, and it might well form a text for nursing and social work courses in the minimum essential medical knowledge.

The first half of the book is devoted to a rapid and, from the standpoint of the physician therefore, a rather superficial review of the standards developed in most part, however, in that it follows precisely the standards developed in the study conducted by the Coöperative Clinical Group and the United States Public Health Service, and in that it often quotes from the works of the currently recognized medical specialists in these fields. The chapters devoted to the communicability of syphilis and gonorrhea are commended especially to those physicians dealing with the genito-infectious disease problem in the schools and in industry, and to all persons interested in the formulation of venereal disease control laws. As the authors point out, it is regrettable that the increasingly frequent practice of employers requiring their employees to have blood tests made and then summarily dismissing those who have positive tests regardless of the age of the infection or amount of treatment given, is supported in many cases by physicians who should know better. And again, when dealing with the problem of communicability, "It is less embarrassing to accuse a toilet seat than to seek for sexual sources, or to request the examination of other members of the family." It requires so much less tact and no labor.

The general public health problem in the management of genito-infectious diseases, though clearly defined, have thus far evoked no generally effective

standard procedures or solutions, as have the purely medical aspects of the problem. In presenting this portion of the field the authors have accordingly seen fit in many instances to express a personal viewpoint which results from their local experience and which, therefore, may not have the advantage of widespread applicability *in toto* at least. It should not be lost sight of, however, that the authors have had as many years of active experience with these problems as have had most health authorities in this country, and that their accomplishments in Massachusetts have brought national recognition.

N. I., JR.

NEW BOOKS.

The Medical Clinics of North America. Vol. 22, No. 4 (*Mayo Clinic Number*, July, 1938). Pp. 360; illustrated. Philadelphia: W. B. Saunders Company, 1938.

The 9 articles of the Symposium on Medical Emergencies will have many absorbed readers. Among the 35 authors is a larger number than usual of well known names.

The Vitamins and Their Clinical Applications. A Brief Manual. By PROF. DR. W. STEPP, Director of the 1. Medical Clinic, University of Munich; Doz. DR. KÜHNAU, Director of the Municipal Institute for Balneology and Metabolism, Wiesbaden, and DR. H. SCHROEDER, Associate at the 1. Medical Clinic, University of Munich. Translated by HERMAN A. H. BOWMAN, M.D., Minneapolis, Minn. Pp. 173, with separate Index of 28 pages. Milwaukee: The Vitamin Products Company, 1938. Price, \$4.50.

The Rheumatic Diseases. A Course of Lectures Arranged by the Medical Staff of the St. John Clinic and Institute of Physical Medicine. Edited by SIR LEONARD HILL, M.B., LL.D., F.R.S., Director of Research, St. John Clinic and Institute of Physical Medicine and Consultant to the Rheumatic Unit at St. Stephen's Hospital (London County Council), and PHILIP ELLMAN, M.D., M.R.C.P., Physician to St. John Clinic and Institute of Physical Medicine and Consultant Physician to the Rheumatic Unit at St. Stephen's Hospital (London County Council). With a Foreword by SIR ARTHUR MACNALTY, K.C.B., M.D., F.R.C.P., Chief Medical Officer to the Ministry of Health. Pp. 270; 46 illustrations. Baltimore: William Wood & Co., 1938. Price, \$4.00.

Outline of Roentgen Diagnosis. An Orientation in the Basic Principles of Diagnosis by the Roentgen Method. By LEO G. RIGLER, B.S., M.B., M.D., Professor of Radiology, University of Minnesota, Minneapolis. Atlas Edition. Pp. 212; 254 illustrations shown in 227 figures presented in drawings and reproductions of roentgenograms. (Figs. 6 to 51 and 55 to 72 are drawings in an original technic by JEAN E. HIRSCH.) Price, \$6.50. (Also Exclusive Text Edition from which the Atlas of Roentgenology has been omitted, but to which all figure references have been retained in the text. Price, \$3.00.) Philadelphia: J. B. Lippincott Company, 1938.

Pathological Technique. A Practical Manual for Workers in Pathological Histology Including Directions for the Performance of Autopsies and for Microphotography. By FRANK BURR MALLORY, A.M., M.D., S.D., Consulting Pathologist to the Boston City Hospital, Boston, Mass. Pp. 434; 14 illustrations. Philadelphia: W. B. Saunders Company, 1938. Price, \$4.50.

The Troubled Mind. A Study of Nervous and Mental Illnesses. By C. A. BLUEMEL, M.A., M.D., F.A.C.P., M.R.C.S. (Eng.). Pp. 520. Baltimore: The Williams & Wilkins Company, 1938. Price, \$3.50.

BOOK REVIEWS AND NOTICES

- A General Textbook of Nursing. A Comprehensive Guide to the Final State Examinations.* By EVELYN C. PEARCE, Sister Tutor, The Middlesex Hospital, etc. Pp. 888; 176 illustrations. New York: E. P. Dutton & Co., 1938. Price, \$3.75.
- Cancer. With Special Reference to Cancer of the Breast.* By R. J. BEHAN, M.D., DR. MED. (BERLIN), F.A.C.S., Cofounder and Formerly Director of the Cancer Department of the Pittsburgh Skin and Cancer Foundation, Pittsburgh, Pa. Pp. 844; 168 illustrations: The C. V. Mosby Company, 1938. Price, \$10.00.
- Life and Letters of Fielding H. Garrison.* By SOLOMON R. KAGAN, M.D. With an Introduction by PROFESSOR JAMES J. WALSH. Pp. 287; 3 illustrations. Boston: The Medico-Historical Press, 1938. Price, \$3.00.
- The Horse and Buggy Doctor.* By ARTHUR E. HERTZLER, M.D. Pp. 322; illustrated. New York: Harper & Brothers, 1938. Price, \$2.75.
- Refraction of the Eye.* By ALFRED COWAN, M.D., Associate Professor of Ophthalmology, Graduate School of Medicine, University of Pennsylvania; Attending Ophthalmologist, Philadelphia General Hospital, etc. Febiger, 1938. Pp. 438; illustrated. Philadelphia: Lea & Febiger, 1938. Price, \$4.75.
- Triumph Over Pain.* By RENE FÜLÖP-MILLER. Translated by EDEN and CEDAR PAUL. Pp. 438; illustrated. Indianapolis: The Bobbs-Merrill Company, 1938. Price, \$3.50.
- Rheumatische Kreislaufschädigungen.* By DR. SIEGFRIED DIETRICH, Dozent für innere Medizin, II. Medizinische Klinik der Charité, Berlin. Mit einem Geleitwort von PROF. DR. G. VON BERGMANN, Direktor der II. Medizin, Univ.-Klinik, Berlin. Band 7, Der Rheumatismus. Sammlung von Einzeldarstellungen aus dem Gesamtgebiet der Rheumaerkrankungen. Herausgegeben von PROFESSOR DR. RUDOLF JÜRGENS, Berlin. Pp. 204; 34 illustrations. Leipzig: Theodor Steinkopff, 1938. Price, Rm. 6.75.
- Verhandlungen der Deutschen Gesellschaft für Kreislaufforschung.* XI. Tagung. Zu Bad Nauheim vom 26-27. März, 1938. Herausgegeben von PROFESSOR DR. EB. KOCH, Bad Nauheim. Pp. 430; illustrated. Leipzig: Theodor Steinkopff, 1938. Price, Rm. 11.25.
- The History of Bacteriology.* (University of London Heath Clark Lectures, 1936, delivered at The London School of Hygiene and Tropical Medicine.) By WILLIAM BULLOCK, M.D., F.R.S., Emeritus Professor of Bacteriology in the University of London. Pp. 422; illustrated. New York: Oxford University Press, 1938. Price, \$3.75.
- The British Encyclopædia of Medical Practice* including Medicine, Surgery, Obstetrics, Gynecology, and other Special Subjects. Under the General Editorship of SIR HUMPHRY ROLLESTON, Bt. G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D., Emeritus Regius Professor of Physicians of London. Sometime President of the Royal College of Physicians in a consultative capacity of F. R. FRASER, M.D., F.R.C.P., G. GREY TURNER, F.C.O.G., M.S., F.R.C.S., JAMES YOUNG, D.S.O., M.D., F.R.C.S. (Ed.), F.R.C.S., F.R.S., F. M. R. WALSHE, O.B.E., M.D., D.Sc., F.R.C.P. Pp. 712; 49 illustrations and 13 plates (5 in colors). London: Butterworth & Co. (Publishers), Ltd., 1938. Price, \$12.00 per volume.
- The more important of the 52 topics treated in this volume are Leukemia (by Janet Vaughan); several aspects of Liver Disease (by R. S. Aitken and others); and of Lung Diseases (by Maurice Davidson and others); Malaria (by Sir S. Rickard Christophe).

Experience in the Management of Fractures and Dislocations (Based on an Analysis of 4390 Cases). By the Staff of the Fracture Service, Massachusetts General Hospital, Boston, under the General Editorship of PHILIP D. WILSON, M.D., Surgeon-in-Chief, Hospital for Ruptured and Crippled, New York; Clinical Professor of Orthopedic Surgery, College of Physicians and Surgeons, Columbia University, etc. (23 Contributors). Pp. 1036; 1417 illustrations of which 1192 are line tracings of roentgenograms in case reports. Philadelphia: J. B. Lippincott Company, 1938. Price, \$15.00.

Applied Anatomy. Functional and Topographical. By ROBERT H. MILLER, M.D., Associate Professor of Anatomy in the University of Tennessee, College of Medicine, Memphis, etc. Pp. 484; 55 illustrations and 16 colored plates. Philadelphia: Lea & Febiger, 1938. Price, \$6.50.

Ueber die Beziehungen der Qualität des Nahrungseiweisses zum Ablauf des Betriebsstoffwechsels. By ADOLF BICKEL, Professor der Pathologischen Physiologie an der Friedrich-Wilhelms-Universität in Berlin. Heft 3, Schriftenreihe zur Schweizerischen Medizinischen Wochenschrift. Pp. 100. Basel: Benno Schwabe & Co., 1938. Price, Fr. 10.

The Healing Knife. A Surgeon's Destiny. By GEORGE SAVA. Pp. 310. New York: Harcourt, Brace & Co., 1938. Price, \$2.50.

NEW EDITIONS.

Internal Medicine. Its Theory and Practice in Contributions by American Authors. Edited by JOHN H. MUSSER, B.S., M.D., F.A.C.P., Professor of Medicine in the Tulane University of Louisiana School of Medicine; Senior Visiting Physician to the Charity Hospital, New Orleans. Pp. 1428; 35 illustrations. Third Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, \$10.00.

Oreille Interne. Etude anatomo-pathologique et clinique Technique, histologique et expérimentale. By CH. CLAUVE (de Paris). Pp. 227; illustrated. Second Edition. Paris: Editions N. Maloine, 1938.

A Textbook of Histology. Functional Significance of Cells and Intercellular Substances. By E. V. COWDRY, Professor of Cytology, in the School of Medicine, Washington University, St. Louis, Mo. Pp. 600; 323 illustrations, some in color. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, \$7.00.

A Textbook of Histology. By ALEXANDER A. MAXIMOW, Late Professor of Anatomy, University of Chicago, and WILLIAM BLOOM, Associate Professor of Anatomy, University of Chicago. Pp. 668; 542 illustrations, some in colors. Third Edition, completely revised. Philadelphia: W. B. Saunders Company, 1938. Price, \$7.00.

Whereas the second edition of this book represented a complete recasting and condensation from the large first edition, this edition has been changed only to accommodate the advances of the past 4 years. The book continues to exhibit the various excellences and shortcomings of its predecessors.

A Textbook of Bacteriology. By THURMAN B. RICE, A.M., M.D., Professor of Bacteriology and Public Health at the Indiana University School of Medicine. Pp. 563; 121 illustrations. Second Edition, revised. Philadelphia: W. B. Saunders Company, 1938. Price, \$5.00.

A few sentences from the Preface explain the nature of the work: "The text remains one for the student and practicing physician . . . the inclusion of a bibliography has been deliberately rejected . . . we have held the morphological and cultural descriptions of the various organs to the real essentials." While it is questionable whether this is the best method to pursue with good medical students, there is no denying the strength of its appeal, and its apparently successful result.

The American Illustrated Medical Dictionary. A Complete Dictionary of the Terms used in Medicine, Surgery, Dentistry, Pharmacy, Chemistry, Nursing, Veterinary Science, Biology, Medical Biography, etc., with the Pronunciation, Derivation, and Definition. By W. A. NEWMAN DORLAND, A.M., M.D., F.A.C.S., Lieut.-Colonel M.R.C., U. S. Army, etc. With the collaboration of E. C. L. MILLER, M.D., Medical College of Virginia. Pp. 1607; 942 illustrations, including 283 portraits. Eighteenth Edition, revised and enlarged. Philadelphia: W. B. Saunders Company, 1938. Price, \$7.50.

In this edition over 3000 new words have been defined, so that the text of the volume has been increased by more than sixty pages. The Index to the numerous portraits and the Index to tables occurring through the text are desirable aids.

A Textbook of General Bacteriology. By EDWIN O. JORDAN, Ph.D., Late Andrew McLeish Distinguished Service Professor of Bacteriology in the University of Chicago. Revised by WILLIAM BURROWS, Ph.D., Assistant Professor of Bacteriology in the University of Chicago. Pp. 808; 197 illustrations. Twelfth Edition, revised. Price, \$6.00.

"The section on oxygen supply and respiration has been entirely rewritten as have those on filtration and the isolation of bacteria in pure culture. A new figure has been added showing the types of bacterial filters commonly used. Perhaps the most extensive revision has been made in the chapter on virus diseases. . . . A section has been added on lymphocytic choriomeningitis and the sections on poliomyelitis and lymphogranuloma inguinale entirely rewritten. . . . Yellow fever has been amplified to include the newly discovered jungle fever. Numerous minor changes have been made such as a reconsideration of the bacteriology of diphtheria, the immunizing properties of typhoid vaccines, droplet infection and others."

Fractures of the Jaws. By ROBERT H. IVY, M.D., D.D.S., F.A.C.S., Professor of Maxillo-Facial Surgery, School of Medicine and Graduate School of Medicine, and of Clinical Maxillo-Facial Surgery, School of Dentistry, University of Pennsylvania, etc., and LAWRENCE CURTIS, A.B., M.D., D.D.S., F.A.C.S., Assistant Professor of Maxillo-Facial Surgery, Graduate School of Medicine, and School of Dentistry, University of Pennsylvania, etc. Pp. 192; 199 illustrations. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, \$4.50.

The Principles and Practice of Medicine. Designed for the Use of Practitioners and Students of Medicine. Originally written by The Late SIR WILLIAM OSLER, BART, M.D., F.R.C.P., F.R.S., Formerly Regius Professor of Medicine, Oxford University; Professor of Medicine, Johns Hopkins University, Baltimore, etc. Revised by HENRY A. CHRISTIAN, M.D., LL.D., S.D., F.R.C.P., Hersey Professor of the Theory and Practice of Physic, Harvard University; Physician in Chief, Peter Bent Brigham Hospital, Boston. (The 9th, 10th, 11th and 12th editions were revised by THOMAS MCCRAE, M.D., F.R.C.P., Formerly Professor of Medicine, Jefferson Medical College, Philadelphia.) Pp. 1424; illustrated. Thirteenth Edition. New York: D. Appleton-Century Company, Inc., 1938. Price, \$9.00.

The Pathology of Diabetes Mellitus. By SHIELDS WARREN, M.D., Pathologist to the New England Deaconess, The New England Baptist, The Huntington Memorial, and the Pondville State Hospitals; Director of Massachusetts State Tumor Diagnosis Service; Assistant Professor of Pathology in the Harvard Medical School, Boston. With a Foreword by ELLIOTT P. JOSLIN, M.D. Pp. 246; 86 illustrations and 3 colored plates. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, \$4.75.

PROGRESS OF MEDICAL SCIENCE

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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IRRADIATION IN CERVICAL CANCER.

Radiotherapy. Five years have elapsed since we have reviewed the subject of cancer of the cervix and it seems that an opportune time has arrived for skimming over the enormous literature that has appeared since that time in order to take stock of the situation as it exists at present. A casual survey of the world literature clearly shows that irradiation is supplanting the radical operation, although in some clinics, mostly foreign, surgical procedures are still employed in some cases.

The material from the irradiation clinic of Doederlein in Munich has been analyzed by Voltz²¹ and presented in a concise form. In the years 1927 and 1928 there were 336 cases of cervical cancer seen of which 20 (5.9%) were not treated because they were absolutely hopeless and died within a few weeks. Of the 336 patients, there were 76 (22.6%) who were well 5 years later, or, excluding the 20 patients who were not treated, the rate of cure was 24%. Dividing the entire series into groups, it is seen that 44 cases in Group 1 showed 26 remaining well; of 88 in Group 2, there were 28 remaining well; of 125 in Group 3, there were 22 remaining well, while there were no favorable results in 79 cases in Group 4. For the period from 1913 to 1928 including the preceding series, there were 2202 cases of cervical cancer admitted of which 163 (7.3%) were untreated. Of this series, 395 (17.9%) were well longer than 5 years after treatment, which equals 19.4% of the patients treated. By groups, the favorable results were 167 of 370 in Group 1; 118 of 489 in Group 2; 103 of 797 in Group 3; and 7 of 383 in Group 4. These figures show relative cures of 45.1% in Group 1; 24.1% in Group 2; and 12.9% in Group 3. Taking Groups 1 and 2 together as representing the operable and borderline cases, there was a relative cure of 33.1%.

From Buenos Aires comes a report by Ahumada, Prestini and del Tognol based on their experience over an 8-year period with 607 patients treated with radium in four different ways, depending upon the type of involvement. They used intrauterine applicators and colpostats where possible, but if the cervical canal had become obliterated, radium needles were inserted into the cervix until a canal could be formed. The primary mortality was 0.3% or 2 cases, 1 from severe hemorrhage and 1 from an accidental injury to the bladder. The cases were closely followed after treatment and showed an absolute cure rate of 28.53%. The relative cure rate after a 5-year interval was 94.1% for Group 1, 40.8% for Group 2, or a combined rate of 46.3% for Groups 1 and 2. In Group 3 the rate of cure was 18.9% while there were no cures in Group 4.

Of 662 private cases of cancer of the female genitalia treated by Schmitz,¹⁶ 80% were located in the cervix. He believes that the extent of the growth of cancer of the cervix is directly related to the curability rate. The time elapsed from the occurrence of the first symptom to the beginning of adequate irradiation apparently does not influence the end-results. The freely movable, clearly localized growth shows from 80 to 90% good results after 5 years. Such growths can only be discovered by routine periodic health examinations. Cancer of the cervix is probably always preceded by a low grade of chronic inflammation. The discovery of chronic cervicitis by follow-up examinations after infections, abortions and labors and its adequate treatment will prevent carcinoma later on. If a silent early carcinoma be found during such examinations and adequately treated at this time, permanent healing may be achieved in nearly every case. In his series of 398 cases there are 90 (22.67%) of 5-year good end-results. Classified according to groups, the analysis shows that in Group 1 there were 36 cases with 31 (87.87%) cures; Group 2 included 53 cases with 25 (47.17%) cures; Group 3 contained 180 cases with 33 (17.78%) cures; while Group 4 contained 129 cases with only 1 (0.78%) cure.

At the Mayo Clinic, according to Bowing and Fricke,⁴ the treatment with radium is by the intensive, broken-dose method, employing in most cases the universal silver tube containing 50 mg. of radium sulphate or 50 mc. of radon. Most patients receive supplemental Roentgen irradiation following the course of radium therapy. In their series of 1491 cases, extending over a period of 15 years, although the great majority of patients (91%) were in an advanced stage of the disease, of the entire number 26.8% lived 5 or more years without evidence of recurrence. The curability by groups was 69.2% for Group 1 and 60.2% for Group 2. That there is little risk to the treatment is shown by the fact that the hospital death rate for the entire series was only 1% and was confined to the group with advanced lesions.

Schreiner and Wehr¹⁷ present a series of 937 cases treated by irradiation at the State Institute for the Study of Malignant Diseases, Buffalo. Their 5-year rate of relative curability was 64.8% for Group 1; 32.7% for Group 2; and 18.28% for Group 3. It can be seen from their report that cancer of the cervix occurs in every period in adult life, the youngest patient being 20 and the oldest being 83, and that there is a gradual increase in the percentages in each 5-year period up to the maximum of 55, and then a decline. They state that not much can be learned

of the extent of the disease from the symptoms as the disease may have been present from a few weeks to several years with almost identical symptoms. A study of the nationality of the patients was of no importance except that there was only one Jewess among 955 patients.

The experience and routine at the Memorial Hospital, New York, have been frequently presented by Healy,¹⁰ who states that in most clinics except his, treatment with radium precedes treatment with Roentgen ray, if the latter is used at all. In a critical review of their cases they were impressed by the high percentage of extensively ulcerated and infected cases coming for treatment in which the adjoining normal tissues were considerably involved in reactionary changes. It seemed highly desirable to them to spend a short time in an effort to prepare the lesion for the application of radium. A great part of the surface growth of these advanced cancers consists of an infected tissue which is very easily destroyed under Roentgen ray therapy alone. Therefore they felt that they might obtain greater regression and a higher percentage of cures with fewer complications if all patients with ulcerated cancers of the cervix were first given high voltage Roentgen ray treatment, together with frequent vaginal antiseptic douches for a period of about 10 days preceding the application of radium. However, in all favorable cases radium is used first, as in such cases there is practically no infection and the lesion is small, the Roentgen ray cycle is then given as promptly as seems feasible after the radium. They believe it advisable to give a second Roentgen ray cycle 8 to 12 weeks after the first series has been finished.

It should be emphasized that external radiation is not used with the idea that it will cause glandular metastases in the deeper portion of the pelvis to disappear since the amount of radiation which reaches the deeper structures is not sufficient to have much effect, but rather it is used because it brings about changes in the connective tissue which help to interfere with the growth and activity of the cancer cell as well as with their lymphatic spread. More specifically, the plan of treatment at the Memorial Hospital consists of: (a) a high voltage Roentgen ray cycle of 4 treatments of 700 R units each; (b) 10 to 14 days later, radium is applied to the vaginal surface of the lesion by means of vaginal applicators for 1000 to 2000 mc. hours; (c) the following day under anesthesia 2 radium capsules in tandem formation are placed in the cervical and supracervical canals for 2000 and 1000 mc. hours respectively; (d) 8 weeks following the first Roentgen ray cycle a second similar Roentgen ray cycle is given. During the treatment and until the cervical lesion is entirely healed the patient is advised to use vaginal douches of potassium permanganate once or twice daily. Interstitial radiation with needles or seeds is not used as a routine but may be used as a later treatment for any portion of the lesion that fails to regress. With the routine use of Roentgen ray first, the appearance of the primary cervical lesion changes markedly, the superficial infected fungating surface disappears, the surrounding edema subsides, the lesion is smaller and the uterus acquires more mobility. The lesion and adjoining tissues are then in much better condition to respond satisfactorily to radium applications and there seems to be less constitutional and pelvic disturbance following radium treatment. While Healy considers irradiation the treatment of choice in most cases of cancer of the

cervix, occasionally surgical treatment is advisable in cases of pyometra which do not respond to drainage and in radiation-resistant cases which seem to increase in extent following irradiation. If pyometra is present when the patient is first seen, a rubber catheter is placed in the uterine cavity for drainage and to permit daily cleansing of the uterine cavity with weak antiseptic solutions, and in the meantime deep Roentgen ray therapy is carried out. If the pyometra subsides, radium is applied in full or divided doses. When pyometra develops as a late or post-radiation lesion, it is best treated by hysterectomy.

Ward and Sackett²³ outline the standard technique which is employed at the Woman's Hospital, New York. In cachectic cases the patient's resistance is improved by preliminary blood transfusions; a small dose of spinal anesthesia is used instead of a general anesthetic if there is no contraindication. They use an initial dose of radium of from 3600 to 4200 mg. hours, depending upon the extent and size of the growth, but in exceptional cases of extensive disease they have used over 6000 mg. hours as the initial dose. As a rule, 100 mg. is placed in the cervical canal and several 12.5-mg. needles are inserted at the junction of the cervix with the vaginal fornix. They stress the importance of distance screening by distending the vagina with gauze to its capacity to keep the bladder and rectum as far away as possible from the radium rays, and they use a self-retaining catheter to keep the bladder collapsed during the radium application. The outstanding feature of their method is the frequent follow-up inspection made by the surgeon himself throughout the 5-year period. During the first 3 years a monthly inspection is made and after that the patient is seen every 2 or 3 months. If the follow-up examination shows a beginning recurrence a further irradiation is given to check it in its incipency. These late irradiations are of small dosage, averaging from 300 to 1200 mg. hours, usually in the form of platinum needles. The results of their 18 years' experience with radium show a 5-year salvage of 27.4% of 595 patients seen and 28.5% of the patients treated. In the cases of early cancer in which the disease was limited to the cervix they saved 56.2%. Of 359 patients seen over a period of 10 years the absolute cure rate was 17.3% and the relative rate was 18%. In spite of lowered life expectancy, 73% of those who survived 5 years lived 10 years or longer. They believe that the extent of the disease is of greater importance than the type of cell in determining the probability of cure, since they found early carcinoma had twice the curability of late carcinoma, irrespective of the maturity of the cells and of whether they were of the squamous or adenocarcinomatous type.

A marked improvement in results has been obtained by Pitts and Waterman¹⁴ since they have changed their technique of application of radium from the simple intrauterine radium capsule to the use of parametrial irradiation by means of multiple needles. They found that they could implant long needles in the parametria and out into the broad ligament and in the vesicovaginal and rectovaginal septum without any difficulties or untoward results. They also found that there was not so much slough and that the cervix returned to normal appearance sooner under this treatment. Their plan consists of placing four 3-mg. needles out into the tissues at the sides of the uterus, 2 needles on each side. They then thrust a series of 2-mg. needles at 1- to 2-cm.

intervals in front and in back of the cervix, using in all from 12 to 16 needles. In the cervical canal they place a 20-mg. platinum capsule, holding it in place with a strand of silkworm gut, or in many cases they still use a tandem of two 50-mg. tubes. They have gradually increased the time of application until now they are allowing the radium to remain from 144 to 168 hours. While there has been a very satisfactory improvement in the results in all types treated, it has been most marked in the cases belonging to Group 3, where the absolute survival rate has increased from 14% under the old method to 29% under the plan of interstitial irradiation. This rate of cure is very high for cancers in Group 3 and therefore their method deserves careful consideration from all who employ radium.

Based upon a study of the world literature from 1912 to 1928, Dietel⁶ states that of 7814 women with *inoperable* cancer of the cervix who were irradiated, 881 (11.3%) remained healed for over 5 years. Subdividing this collected series he found that healing occurred in 9.9% of those who were treated with radium alone, in 10.5% of those only receiving Roentgen therapy and in 13.4% of those receiving combined radium and Roentgen ray treatment. It would appear, therefore, that the combined treatment offers the best results, and of the various methods of combined treatment, he believes that the technique of the Heidelberg Clinic surpasses the others. This method consists of an intensive Roentgen irradiation of the parametrial tissues after the application of a full dosage of radium, taking precautions to avoid injury to neighboring organs.

Operation Combined With Irradiation. Since 1919 at the Cancer Institute in Ghent, Belgium, Daels⁵ has been experimenting with the problem of applying radium to the uterus after exteriorizing the pelvis by surgical operation. After making a low transverse abdominal incision, the lower edge of the peritoneum is sutured to the skin above the pubis and inguinal canals. The peritoneum of the posterior wall of the pelvic inlet is incised transversely to the mesosigmoid, the upper edge of the peritoneum sutured to the anterior parietal peritoneum, the lower edge sutured to the upper edge of the skin incision. In this manner a new pelvic diaphragm is made at the level of the sacral promontory which closes the peritoneal cavity from the pelvis, and the radium can be applied to the various parts of the pelvis under direct vision. The pelvic organs can be irradiated with an even distribution of the rays, there will be no injury to the connective tissues, a longer application and a stronger dose can be given and any infected secretion will have an easy outlet. If better exposure be desired the infundibulopelvic ligaments can be cut or an easy hysterectomy can be done because the clamps can be left in place. The implantation of radium is not done until from 3 to 5 days after the operation has been performed, packing off the bladder and rectum with gauze-covered lead plates, 1 to 2 mm. thick. In the first 20 cases treated by this method there was only 1 death and that was due to a severe infection. More recently, in order to irradiate the pelvic lymph nodes, he has been using curved metal tubes in which radium can be placed and spaced. The tubes are of different sizes and curved, so that they can be brought into apposition with almost any part of the pelvis. In introducing these tubes a short low midline incision is made and the fingers introduced for the purpose

of orientation. The curved tubes are then introduced through lateral abdominal stab wounds and placed by the sense of touch of the fingers within the abdomen. Usually 2 tubes are placed in each side of the abdomen.

In the plan advocated by Gellhorn⁸ the abdomen is opened by a mid-line incision, the intestines packed away and the pelvic cavity is exposed to sight and touch. The operator inserts the index and middle fingers of his left hand beneath the sterile drappings into the vagina, and proceeds to do a bimanual examination with the other sterile hand inside the abdomen. It is astonishing how much one can learn by this sort of examination. The extension of the cancer is almost always found to be greater than was assumed before the operation. After this exploration, gold seeds containing radium emanation are inserted beneath the peritoneum in such a way that these seeds form a complete ring around the periphery of the cancerous area. The guiding fingers in the vagina not only help in selecting the places where the seeds are to be introduced but also make it possible to gauge the exact depth to which the needles have to be pushed. The operator then withdraws from the operating table while an assistant closes the abdomen. The patient is then placed in the lithotomy position and the operator inserts one or more capsules of radium into the uterine cavity and radium needles into the tumor itself, particularly its outer edge. The total irradiation amounts to between 4200 and 4500 mg. hours, over one-half of which is obtained from the gold seeds. The peritoneal reaction is no greater than after any laparotomy and the small gold seeds produced no local necrosis nor irritation as foreign bodies.

In the borderline cases of cancer of the cervix, Taussig²⁰ frequently combines irradiation with surgical removal of a large portion of the tributary lymph nodes. Careful selection of the cases must be made as the patient must be a good operative risk and should preferably be of the younger age group. Of his 46 patients, the average age was 41 years. His plan consists of giving 1000 to 1500 R units of deep Roentgen ray therapy spread over 2 weeks. Two weeks after this series is concluded iliac lymphadenectomy is done under spinal anesthesia. Two weeks after the operation an intrauterine application of 4000 to 5000 mg. hours of radium irradiation is given and this is followed by an additional 2000 to 2500 R units of deep Roentgen ray therapy. The difficulties of the operation are not great and thus far he has not injured the large vessels although the dissection approximates them closely.

Comparison of Operation With Irradiation. The opinion of Shaw,¹⁹ of England, as to the relative value of operation and irradiation in the treatment of cancer of the cervix is of great interest because he has been identified with the first operations of the kind which were done in Manchester. Although the time consumed in performing the operation has gradually been reduced until now it is only an hour in favorable cases, he considers the operation the limit of human endurance. He believes that every operator has to acknowledge a mortality of 20% in his first 100 cases, though the rate steadily improves with experience. In his last 20 cases he had only 1 death and of his entire reported series of 154 cases there was an operative mortality of 21.4%, with

38.3% alive and well after 5 years. In comparison with these figures he has treated 94 cases with radium alone, with 41.4% alive and well after 5 years. It seems to him, therefore, that he is getting the same percentage of cure with radium as with the radical operation, but with this great difference, namely, that the radium cases include advanced as well as early ones, while the operation list includes only the early and borderline cases. Even if the results with radium were just as good and no better than those with operation, he feels that radium would be the treatment of choice. There is such a slight mortality and the convalescence is painless, whereas after Wertheim's operation a large percentage of the patients are very ill for some days, and at the best are very slow in their recovery. The value of these figures lies in the fact that they are from one clinic and are free from personal bias. Although Shaw is well qualified to perform the radical operation and has had much experience with it, he has come to the conclusion that radium offers the best chance of cure and is the more humane method of treatment.

In the gynecologic clinic at Kiel, according to Schroeder,¹⁸ there were 604 cases of cervical cancer under treatment from October, 1922, to December, 1930. Of these, 50% were operated upon, 178 by the Wertheim operation and 124 by the Schauta method. The primary mortality of the Wertheim cases was 18% while the Schauta group had a 1.5% mortality. The curability rate was 36% for the Wertheim group and 51% for the Schauta group. There were 253 cases treated with radium, of which 51 were in an operable stage. Of the operable group, there were 42% cures, while of the 202 inoperable cases 10% were living at the end of 5 years and there was a primary mortality of 16.5%.

Another comparative series has been presented by Plate¹⁵ from the gynecologic clinic at Amsterdam with results that also confirm that radium should supplant operation. Of 193 cases in this series treated by radium, 72 were well after 5 years, a curability rate of 37.3%, whereas of 70 patients subjected to the Wertheim operation, 22 (31.4%) were well at the end of 5 years.

Mortality Studies. From the Mayo Clinic comes a report by Fricke⁷ based upon 1117 patients who were treated by radium and Roentgen rays. Of these, 13 died during the primary course of treatment, a primary mortality rate of 1.16%. Comparison of the findings at necropsy of patients who died during the first course of treatment and of those who died during subsequent visits disclosed that acute pelvic infection and hemolytic streptococcic septicemia accounted for most of the deaths in the first group. A rather unexpected finding was that there were as many patients with metastases to the lymph nodes in the first group as in the second, and that there was a greater number with distant metastasis in the first group than in the second. Distant metastases occurred mainly to the lungs and the liver, were unsuspected and by present clinical methods were undiscoverable. From this study he believes that the prognosis in every case accepted for treatment must be very guarded. The relatives must be instructed that distressing complications may occur and that these complications often terminate fatally, even though the patient appears to be in good general

health. The best method of keeping the mortality rate as low as possible is by thorough study of each case and with suspicion of metastatic involvement or of impaired renal function, to limit treatment so as not to place undue stress on the patient. Such patients should be treated for palliation and not for cure. The broken-dose method of treatment seems preferable to the massive-dose technique, the effect appears to be gentler and on the appearance of any serious complication, irradiation may be instantly abandoned.

The histories and necropsy records of 166 patients who died from cervical cancer in the Philadelphia General Hospital have been studied by Behney,³ who found that only 7 (4%) died from causes which were not dependent upon the presence of cancer. In the older patients, death was caused by secondary infection twice as frequently as in the younger ones. In the latter group, death was more often the result of some mechanical cause such as obstruction of the ureters or hemorrhage. The more anaplastic the type of tumor, the more frequently did metastasis occur. Involvement of the pelvic sympathetic nerves was demonstrated and he suggests that this involvement may be a factor in the production of pain and perhaps the interruption of impulses through these nerves by invading tumor cells may be the explanation for the occasional spontaneous disappearance of pain in patients with advanced disease.

Morton¹² studied 36 autopsies upon women in whom cervical cancer had been treated by irradiation. It was found that cases which were advanced when first seen usually died because of the local extension and that metastases were frequently absent. Patients adequately treated lived longer and death was due more often to metastatic lesions, probably because the local growth was held in check while metastases had time to occur, or those already present had time to mature and kill the woman. In the inadequately irradiated patients, the local growth was usually responsible for death.

Histologic Studies. From their studies at the Memorial Hospital, New York, Arneson and Stewart² emphasize the necessity of increasing the dose of Roentgen rays to the parametrium if any marked improvement is to be made in the cure of cervical cancer. They studied the clinical and pathologic changes occurring following different amounts of external irradiation delivered to the primary tumors of the cervix, with the hope that they might prove an index of what was going on in the parametrial extensions. They found that the quantity of external irradiation introduced into the primary tumor by the methods so far employed will not cure more than a very small percentage of cervical cancers and therefore cure of parametrial disease is equally rare. Furthermore, it is unlikely that the usual dosage which is applied to the parametrium will lead to any marked restraint in growth in the average case. On the other hand, there is both clinical and histologic evidence of marked regression of the primary lesions, even if cure is not obtained. There is a very decided difference in the dosage which will produce marked regression clinically and that which will produce complete histologic sterilization. The question arises whether under such circumstances it is worth while to pursue a protracted course of external radiation. They believe that it is, not because it will result

in a decided increase in the curability of the average cervical cancer, but because it may be a factor of importance in an occasional case. There is a large gap between the 3.2 threshold erythema doses delivered by the present methods and the 6 to 8 threshold erythema doses which they found most effective in radium treatment of the average primary cervical cancer. It is possible to close this gap partially if one is willing to accept a greater degree of initial cutaneous reaction and rectal and vesical irritation as the dose delivered by external irradiation is increased. Although this may be unwarranted in favorable early cases, it seems well warranted in borderline and advanced clinical cases in which conservative methods have little to offer.

In discussing the relationship of histologic structure to radiosensitivity, Norris¹³ states that this relationship is a complicated one owing to the fact that so many factors enter either directly or indirectly into the question. Among these may be mentioned the location of the tumor, its accessibility, the character of its bed, the distance, and the type of intervening tissues; whether the neoplasm is papillary or infiltrating; the character of its blood supply; whether the blood-vessels possess thick or thin walls, their situation, whether central or peripheral, the general vascularity of the new growth, the size and perhaps the shape of the neoplasm, the character of the tumor cells, the degree of maturity, the proportion of immature cells, the relative number of cells undergoing mitosis, the amount of adipose tissue present, the rapidity of growth of the tumor, the relative amount of fibrous tissue and the desmoplastic property of the neoplasm; whether or not there has been previous irradiation, the presence of infection, the general condition of the patient, her age, the presence of syphilis, tuberculosis or trauma caused by earlier operative procedure, the degree of anemia, cachexia, or ischemia, hereditary influence of the tissue from which the tumor had its origin, the presence of metastases and perhaps even the social status of the patient. Intensity of irradiation, dosage, distance, filter, duration of exposure and other factors also enter into the problem. It is apparent, therefore, that the entire subject of radiosensitivity of tumors is so complex and influenced by so many factors that positive conclusions regarding individual cases are difficult of attainment. It is generally conceded that the degree of anaplasia and the amount of mitosis are definite factors in producing radiosensitivity and yet it is well known that both may vary markedly in different sections of the same tumor. When considered in large groups he believes that a certain amount of dependence may be placed upon histologic grading, but when applied to individual cases this becomes extremely uncertain. In general, papillary tumors are more sensitive than are those of the infiltrating type. It is probable that the type of circulation is an important factor in determining radiosensitivity. Neoplasms that are soft, friable, highly vascular and of the papillary type usually undergo marked regression and disappear rapidly under suitable irradiation. Hard, infiltrating tumors within the cervical canal seem to be much more resistant.

Complications of Irradiation. Attention has been directed by Jones¹¹ to a new clinical entity that may develop and call for surgical intervention months or years after complete regression of the cervical cancer.

This condition is a benign stricture of the intestine—that might easily be confused with metastatic carcinoma. The rate of recurrence of cancer is so high that almost any abdominal or pelvic pain may be attributed to malignant extension or metastasis. If the condition is actually a benign stricture caused by irradiation, it is quite obvious that additional Roentgen ray treatment would only aggravate the condition. Therefore, one should always keep in mind the possibility that a patient who exhibits unusual abdominal disorders, particularly if they simulate intestinal obstruction, several months or even years following radiation therapy, may have a stricture of the intestine and may be restored to normal health by resection of the lesion. Before this disability is attributed to metastasis, thorough reexamination by sigmoidoscopy and roentgenographic studies should be made to eliminate the possibility of this curable complication. While Roentgen examinations demonstrate lesions in the sigmoid quite readily, strictures in the small intestine are quite difficult to visualize unless the obstruction is practically complete. In this type of case it is inadvisable to give barium in any large amount and therefore exploratory laparotomy is warranted, especially in patients in whom there is no evidence of recurring carcinoma in the pelvis. As to the cause of these strictures, Jones believes that the initial insult is delivered by radium. If a loop of small or large intestine remains in the same position in the cul de sac during the entire time of radium irradiation, the erythema produced at this point may be sufficient to produce a simple local peritonitis which would fix the bowel at this point temporarily, and before the exudate is completely absorbed, Roentgen rays are administered, thus furnishing additional irritation, which is sufficient to cause an ulceration in the mucosa that eventually goes on to stricture formation. As time passes, the exudate is absorbed and the bowel becomes free, which is the general finding at operation. To prevent this complication, a change of position of the patient during the treatment suggests itself as an aid, but this would not be entirely safe, for fear of dislodging the radium tubes and possibly causing damage to the rectum or bladder. However, a Trendelenburg position maintained during treatment may help to keep the intestine out of the pelvis while the latter is being irradiated both by radium and by Roentgen rays. If the theory of some fixation of a loop of intestine is tenable, drugs to stimulate peristalsis may be administered and he believes that it might be advisable to give from 0.5 to 1 cc. of pitressin every 4 hours while the radium is in place in order to keep the intestine moving, and thus to preclude excessive irradiation of any one loop.

Complications affecting the urinary organs are discussed by Graves, Kickham and Nathanson.⁹ They state that there are two types of radiation reaction within the bladder. First, there may be the early or acute reaction which occurs at the height of the radiation effect in the cervix itself. This varies in degree, gives rise to symptoms of cystitis and either subsides or goes on to ulceration or even fistula formation. The late radiation reaction results from vascular changes which may vary in degree from mild transient interference to complete obliterative endarteritis with ischemic necrosis, and the lesion produced in the bladder will depend upon the extent of these effects. The symp-

toms consist of dysuria, hematuria and increased frequency, occurring long after the treatment of the cervix. Clinical differentiation between a late radiation reaction and invasion by tumor may be difficult and sometimes cannot be made by the cystoscopic picture alone. A history of radium treatment of the cervix followed by a prolonged interval of many months before the appearance of the bladder lesion favors the diagnosis of radiation reaction. In every instance of late radium reaction in their series, radium seeds, occasionally glass but usually gold, were used in the treatment of the cervix. They believe this to be of great significance, since inadequate filtration and the site of insertion in the periphery of the growth undoubtedly play the greatest part in the production of this complication. Obstruction of the ureters is another frequent complication, since they found it present in 70% of 257 cases of cervical cancer. Because of this they urge that complete urologic investigation be included in the management of this disease. In this way, measures of relief may be made available for the pain and distressing symptoms of uremia which so often confront these patients. Such measures of relief may be simple dilatation of the ureter by means of a catheter, nephrostomy, ureterostomy or nephrectomy, according to the severity of the case.

In the experience of Ward,²² upper urinary tract disease was usually a late development and generally due to obstruction of the ureter, which could usually be demonstrated by catheter at about 4 cm. from the ureteral orifice. The action of radium which produces a proliferation of connective tissue with subsequent contraction is responsible for the complication in many cases, due to the proximity of the ureters to the sides of the cervix as they pass through the base of the broad ligaments, although the invasion of the carcinoma into the same region is a frequent cause. He urges that in the follow-up of these patients we should watch for urinary disturbances, as the early discovery of ureteral stricture may allow of its being relieved by simple dilatation, or if necessary a nephrectomy may be done.

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DERMATOLOGY AND SYPHILOLOGY.

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 SYPHILIS IN INDUSTRY

A REVIEW OF PROBLEMS AND POLICY.

THE rapid development of the public health campaign against syphilis in this country has precipitated the disease upon the lap of industry with a suddenness probably as disconcerting to industry as to the victims of the infection. Inevitably every unforeseen or difficultly controllable contingency in the general campaign mirrors itself in varying grades of miniature in the problems and methods of the industries which have taken cognizance of the matter. The first consideration on which investigation and writing have been active for a quarter-century, is that of the industrial prevalence of the disease.

Prevalence of Syphilis in Industry. In offering the following series of estimates, account should be taken of the fact that they are based almost entirely upon the use of a single uncovering method; namely, blood serologic tests. They will inevitably, therefore, reflect the problems of false positiveness and false negativeness, and of artificial selection (as in the avoidance of industries known by syphilitic or non-syphilitic workers to require blood tests as conditional to employment). One of the earliest American studies of occupational distribution of syphilis was that of Stokes and Brehmer²⁵ at the Mayo Clinic (1920) in which the examination of 1143 Mayo Clinic patients, classified by occupation, disclosed 11.7% syphilis in railroad employees, 6.1% in laborers, 3.8% in merchants and tradesmen, and 1.5% in farmers. In 1921, Williams²⁸ reported 4.4% syphilis in apparently healthy applicants for work. The medical service of a manufacturing company,²² in 1923-1925, reported among skilled, semi-skilled and clerical workers to the number of 3447, an incidence of 3.5% syphilis. The Endicott-Johnson shoe manufacturing interests,¹⁴ in 1928, reported 3.7% syphilis in 4117 workers. The Seattle City Health Department⁵ found in 1927-1931, among milk-handlers and drivers of public conveyances, 3.7% syphilitic among 26,408 persons. The City Health Department of San Francisco⁵ in 1930, among 700 examinations, found 4% syphilis in milk-handlers. Barbers in Oklahoma,⁵ in 1930, rated 13% syphilis. A West Virginia coal company,⁵ in 1931, reported 8.5%

syphilis among 4448 employces, which included 5.1 % among American whites, 16 % among American negroes, and 6.4 % among foreign-born employees. In Minnesota, the Employment Stabilization Research Institute⁵ in 1931 reported, among unemployed casual laborers, 8.4 % syphilis in 227 examinations. Parran^{20a} quotes the following figures, based on collected data of the Office of Industrial Hygiene of the Public Health Service, and material obtained by members of the Association of Industrial Physicians and Surgeons, as reported in Detroit, May 19, 1936. Of 15 companies making routine blood tests in a total of 80 companies represented, 4.8 % syphilis was found among 110,675 employees. Among 21,239 applicants for positions, only 2.3 % were positive, which Parran believes indicative of the tendency on the part of industrial workers to avoid occupations where routine blood tests are to be expected. The Eastman Kodak figures^{20a} among 4000 applicants are given as 1.1 % syphilis. Nine railroads requiring tests on routine applications for jobs gave among 21,026 applicants, 7.8 % syphilis.²⁰ Some of the railroads, possibly because of their geographic situation, reported considerable lower percentages (5 %, 4.04 %). The E. I. duPont de Nemours Company,⁹ among 36,794 employees, reported 4.2 % positive blood reactions for syphilis. The U. S. Coast Guard²¹ shows an interesting differentiation between personnel in the sea service and the life-saving service; 5.7 % in the former and 0.4 % in the latter. Long,¹³ from the medical service of the Gulf Refining Company, Port Arthur, Texas, reported 32 % positives in 900 negroes, and 5 to 10 % positives in 1400 tests on whites. The Caterpillar Tractor Company (Vonachen²⁷) disclosed 4 % syphilis in 9450 employees.

From this résumé, by no means complete, it is clear that the incidence and prevalence of syphilis varies markedly with occupation, with race, and with the geographic location of the industry. For instance, agricultural and industrial labor in the South runs high in syphilis (12 to 35 %) according to the U. S. Public Health Service surveys.¹² It is therefore clear that any industry which draws from a population type such as the negro, in which the incidence of the disease is intrinsically high, will inevitably reflect its prevalence.

The Cost of Syphilis to Industry and Labor. Figures of this sort have still a somewhat speculative character. Many of them are old and possibly outdated; based on individual surveys of industries whose identities are concealed and whose representative character for the problem in general or the country at large cannot be determined. Among the most quoted estimates are those of Parker¹⁹ (1932), including 12 % syphilis in a group of railway employees exhibiting delayed convalescence and disability whose total loss of time represented 13,946 days, and \$48,711. A large industrial concern, unnamed, whose personnel efficiency had dropped below expectations, found that 1 in 10 employees had gonorrhea or syphilis, 68 % of the non-effective employees were on the sick list because of these diseases, and those venereally diseased had lost three times as much time as persons not affected. Each person with syphilis or gonorrhea was paying out an average of \$75 a year for such treatment as was being given. The establishment of a clinic within the industry for adequate treatment and assistance to these persons presently offset the cost of the establishment by increased production. A West Virginia manufacturing

concern, as a result of the installation of a clinic for venereal disease costing \$5000 to \$6000 for the first year, sustained an increased efficiency of 35 %.

It is clear from a review of the literature that statistics providing adequate differentiation among types of employees, types of industry, and obtained by methods other than mere routine serologic testing of blood, are really needed before the problem can be envisaged in its entirety, and principles formulated.

The Kind of Syphilis in Industry. It is a notable fact, one of the first items in the primer of modern syphilology, which is as yet so unfamiliar to many, that the kind of syphilis that a person has rather than the mere fact that he has syphilis, is of major importance. The effort to differentiate syphilis into its industrially and medically significant and insignificant phases has thus far made very little progress. To the syphilologist, the blood testing of employees is no more than the merest first step; competent medical examination of the candidate for employment or the employed person is the only means by which infectious syphilis will be differentiated from non-infectious, and syphilis which is industrially dangerous can be separated from syphilis which is a liability, but not a danger. The expectation, of course, must be that serologic uncovering methods will disclose an enormous amount of latent syphilis of which the victims are in general entirely unaware. Those writing on the subject have no difficulty in supplying harrowing case incidents of deserving employees discharged after years of useful service, merely upon the basis of a single positive blood test. The current possibilities of misapplication or unjust discriminations based on blanket legislation covering such groups as food-handlers is also obvious to any syphilologist. A worker in the laboratory of a milk-handling concern, though he never have contact with milk, can be ruled by a State Attorney General to come under the law covering blood tests for food-handlers, and be discharged from his occupation in a food-handling industry even though he has absolutely no connection with the handling of food. The differentiation of congenital from acquired syphilis, the evaluation of late latency by the spinal fluid examination, now one of the most essential of all tests for the determination of the kind of syphilis which is significant to both patient and job, has thus far made very little headway. The Baltimore and Ohio Railroad, for example, as reported by Milholland,¹⁶ does spinal fluid examinations in selected cases.

Moore,¹⁷ in his editorial expressions on this problem, has pointed out that syphilis of the cardiovascular and nervous systems (to which might very properly be added that of the special sense organs) is the industrially important and differentiable phase of the disease to which industry should turn its attention. How extremely important the adequate differentiation of syphilis from the standpoint of serious involvement may be for an industry is well illustrated from the study of Cochems and Kemp.⁴ Dividing a group of 1000 employed syphilitics into two divisions on the basis of physical strain imposed by their occupations, they show quite clearly that the intermediate and heavy occupations markedly predispose to the incidence of cardiovascular syphilis, and that the employer may therefore expect, from non-recognition of the syphilis in this group of employees, to reap a very sig-

nificant harvest of industrial disability and possible compensable injury actually due to the development of cardiovascular syphilis on the job in unrecognized victims of the disease. Studies such as this are notable for their scarcity in the current literature which apparently consists largely of a rehash of old figures, many of them now quite outdated by the advance knowledge, and devoid of the painstaking analysis which alone can make them practically useful or thoroughly convincing to the hard-headed employer.

Efforts to Define an Adequate Industrial Syphilis Policy. Special interest attaches to the pronouncements of officers of the U. S. Public Health Service, on whom falls so large a responsibility for initiative in the effort to control syphilis in this country. Parran^{20b} (1937) outlined the following essentials for an industrial policy consonant with the public health aspect of syphilis, as follows:

1. That routine blood tests are desirable for applicants for employment.

2. That routine blood tests are desirable at the time of periodic examinations of employees.

3. That industry, with its compact organization, will find the development of a vigorous educational campaign profitable.

4. That industry might extend that educational program into the field of prophylaxis.

5. That there is a responsibility upon the industrial medical officer to see that adequate modern treatment is available to employees at prices ordinary wage-earners can afford, and if such is not otherwise available, the industrial medical service should itself undertake such treatment.

6. That syphilis must at all times be handled as merely another communicable disease. The privacy of relations between the worker and the medical service should be conducted in the best professional tradition. In ordinary cases, it cannot be regarded as grounds for the rejection of applicants or for the dismissal of employees, though treatment may be properly required.

An important contribution by Sayers,²³ of the division of Industrial Hygiene of the National Institute of Health, lays a foundation of principles with reference to the significance of syphilis for various types of occupations, which should be quoted. Sayers points out that while broad administrative policies may be defined, the decision as to what shall be done about syphilis in the employee and the industry must be based upon consideration of the individual case. In doing this, two groups of variables appear: (1) The particular job, its requirements and responsibilities; and (2) the particular syphilitic, the stage of the disease and the treatment taken. When one considers the job, there seem to be four principal sorts of human relationships involved; three of these concern industry. The other, or the individual job, is more or less distinguished by the fact that it is not integrated into a larger enterprise, such as the job of the farmer, the artist, or the prospector, for example. Sayers divides jobs as follows: First, the personal contact job, in which it is important to keep alert for early syphilis. Among these he classes food-handlers, hotel workers, barbers, beauty parlor workers, Pullman porters, matrons, nurses and school teachers. He might well include all classes of domestics. His second

classification is the job of responsibility: Air pilots, engineers, operators of switches, train dispatchers, crane operators, financial executives, for example. Among these, late syphilis as recognized by special tests and special examining acumen is highly significant. The third classification is that of the routine job such as clerical workers, laborers and so forth, in which he rates syphilis as of less importance, but still a factor.

The general survey of the literature leaves the reviewer of industrial syphilis problems impressed with the need for a more elaborate statement of the principles foreshadowed by Parran and Sayers. This may be derived from a survey of experience and literature, as follows:

1. More critical attention should be given to flaws in the serologic uncovering mechanism. The extent to which it is being used and a rather general unfamiliarity with its limitations calls for a general campaign of medical and public education on interpretation, as well as improvement and critical evaluation of facilities. Particularly is it essential that those who deal with industrial syphilis shall understand the following:

- (a) Serologic tests do not establish or negate *infectiousness* in the individual case. Inasmuch as its infectiousness is one of the principal reasons for detecting and dealing with syphilis in industrial aggregations, this important defect should be clearly understood. It should be especially kept in the foreground in dealing with Sayers' first group of personal contact jobs.
- (b) Serologic tests are only as dependable as the laboratory which performs them. The importance of false positives as well as false negatives has been brought to the front by recent public health service surveys of national extent, a fact which is apparently not yet sufficiently understood by those responsible for the taking of blood tests on employees. Individual industrial laboratories should be subjected to the same tests for efficiency and reliability as are being planned for state, hospital and other laboratories issuing reports on serologic tests for syphilis. It should be clear to all users of the serologic uncovering mechanism that a single positive Wassermann requires repetition for confirmation. Moreover, the more serologic tests are taken, the more important it is that the laboratory performing them be under constant control and thoroughly reliable. The proposal, for example, to repeat serologic tests at each employee reexamination (Moore) will definitely increase the possibilities of confusion from so-called "serologic discords" and from partial or weakly positive reactions in persons who do not have syphilis, as well as false negatives in those who do. In this connection, the work being done on syphilis reagin in the blood of normal persons and the unreliability of provocative tests should be made thoroughly familiar to industrial physicians and the heads of organized industrial medical services.
- (c) Serologic tests performed "in the air" by clinically uncontrolled laboratories have a serious element of unreliability. The serologic test is not the court of last resort in the deci-

sion as to whether or not individual patients have syphilis. It is essential that laboratories performing serologic tests have clinical contacts and syphilologic control, as well as interlaboratory checks. Any industry which undertakes to set up its own laboratory service should set up side by side with it or arrange for an adequate clinical service under syphilologic specialist control to keep its blood test uncovering mechanism with its feet on the ground.

2. The detection of syphilis by a blood test, properly confirmed, is an immediate occasion for further study of the case to determine (a) infectiousness, (b) involvement of the nervous system (spinal fluid examinations), (c) cardiovascular disease, which in many cases is materially assisted by a competent cardiologic service, and (d) special sense organ involvement. It is obvious that facilities for the performance of spinal puncture and immediate examination of the spinal fluid are as important to the industry undertaking to evaluate syphilis, as is the original blood test mechanism. Contact should be made by industries with competent specialists to assist in the further evaluations required. It should be pointed out that mere reliance upon specialists, however, is not sufficient. The industrial physician himself must know the clinical manifestations of syphilis, and be prepared to recognize them as part of the routine physical examination on the applicant or employee. This is especially important in cardiovascular syphilis and frequently of great significance in neurosyphilis. Garner,⁸ on the basis of published summaries, laid some emphasis on this point.

3. To the Reviewers, it would seem that Sayers' important emphasis on questions of infectiousness deserves more expanded treatment. The importance of syphilis is proportionate to (a) the opportunity which the industrial syphilitic has to spread the disease. It is not proposed to limit this conception of his infectiousness to contacts taking place merely in the routine performance of his industrial duty. It is a concern of the employer, for example, that the waitress in the company restaurant, who is acting as a disseminator by clandestine prostitute activity with employees, shall be rated as an industrial hazard, precisely as is the employee who handles the lettuce or passes a towel from one person to another. Smith²⁴ has emphasized the practical importance of the intramural carrier in a large group centering about a small industrial plant employing young men and women. This plant was 30 miles from the clinic. Fifty-seven names of exposed persons were obtained by messages of patients and correspondence. Twenty-four persons were examined in the clinic; 9 gave negative reactions and 15 were found to have acquired syphilis. In fact, it is quite conceivable that the syphilis transmitted through the intramural sexual contact of syphilis-infected employees is a more important issue than the transmission of syphilis through the mediation of food, articles of common use and the like. Much of the current emphasis on food-handling transmission of the disease is an unwarranted extension to an entirely different field, of conceptions appropriate to typhoid fever, scarlet fever, undulant fever, amebic dysentery, and so forth, among food-handling employees. The amount of syphilis disseminated by a waitress through a sandwich or a dish is really of no significance whatever, as compared with her activities through other forms of "personal

contact." Sayers' second principle may be rephrased and expanded by giving as item (b) the key importance of the person with syphilis. This allows consideration for the workman at a high-speed tool whose slowly failing vision causes the ruin of an important piece of work, quite as much as it does for the engineer whose cerebrospinal involvement carries him past a red semaphore or leads to the ignoring or misinterpretation of an order. The third item (c), determining the classification of syphilis as an industrial liability, is the possible cost of an individual syphilitic person's disease to the industry in which he is employed. In this classification falls, for example, the important relationship between syphilis and trauma, to which notable contributions have been made in this country by Klauder and Solomon¹¹ and by Klauder.¹⁰ A footnote to Klauder and Solomon is worth quoting almost in its entirety:

"The workman with dementia paralytica engaged in a hazardous or responsible position jeopardizes his own life, that of his fellow workmen and others. His menace in industry and to society need not be emphasized. From data compiled by Pollock and Nolan (State Hospital Quarterly, May, 1923) they give 804.7 as the rate per hundred thousand of dementia paralytica among captains, masters and pilots in the State of New York; 350.6 for telegraphers; 275 for railroad conductors; 238.7 for locomotive engineers; 202.7 for switchmen, towermen and flagmen, and 186.0 for brakemen and trainmen. Lansburgh (Labor and Industry, 13: 3-7, 1926 Commonwealth of Pennsylvania Department Labor and Industry), writing on the worker's responsibility in prevention of accidents, comments on the humorous incident of the man who saved off the limb of a tree on which he was sitting, and points out that in Pennsylvania, in 1925 a worker actually did saw himself off the limb of a tree. . . . Again, Garner (South. Med. J., 19: 222, 1926) records the following: An autopsy performed upon one man who lost his life in an accident, disclosed a severe syphilitic brain lesion."

Camp,³ Stokes and Brehmer and others cite specific instances in which neurosyphilis was unquestionably responsible for serious railroad accidents, and Parran gives one such example a highly personal and vivid touch. Speaking from the industrialist's side, both Klauder and Solomon, and Klauder point out that industrial compensation laws now abolish the defense of contributory negligence; hence it is no defense for the employer to show that preëxisting disease brought about accident. In fact, Klauder's contribution on interstitial keratitis and trauma should be read by every industrial physician, and its principles become familiar to industrial executives and medico-legal counsel.

Eliet,⁶ under the professorship of Jeanselme, laid down in 1926 a summary which is constantly quoted by persons concerned today with the influence of trauma in syphilis (Beeson²). His classification of its effects includes: 1, a single and violent trauma; 2, a single mild trauma; and 3, mild trauma repeatedly applied. For all of these the industrial physician should be constantly on his guard in evaluating the potential significance of syphilis in an employee for his company. The importance of complete evaluation in the syphilitic patient from the standpoint of asymptomatic neurosyphilis must be particularly stressed in this connection, for employees with negative serologic tests and a history of treatment in which evaluation of the status of the nervous system has been overlooked can furnish some of the most startling and serious examples of the activation of nervous system involvement by

trauma (*Urechia*²⁶ and Barthélemy¹). It should be pointed out also that the question of infectiousness is entangled with the trauma issue, and that *Spirochaeta pallida* may appear in early syphilis in lesions induced by vesicants and other traumatizing agents (Frankl,⁷ 1936). Neisser,¹⁸ of course, observed this in the skins of syphilitic patients, in whom no trauma was present. Some of the practical aspects of this problem as it affects industry have been summarized by May.¹⁵

4. The employability of a person with syphilis depends on Items 2 and 3 as outlined above, and not on the mere fact that he has syphilis. It is at this point that most of the adverse criticism of industry for the discharge of an employee merely upon the discovery of what is actually a completely harmless syphilis, is directed.

5. Industry will find it a duty and a profitable one to care adequately for the types of syphilis involved in (3), (a), (b) and (c). Most of the statistical estimates on which this statement would have to rest are still not too well defined; they foreshadow, however, a comparatively easy demonstration of the profitableness of a treatment, as well as a case-finding mechanism as an investment for almost any industry. This possibility is clearly foreshadowed in Parran's Item 5 in his declaration of public policy.

6. For the relatively large proportion of latent and inactive syphilis which a case-finding mechanism in industry will detect, industry itself will be wise to take a responsible attitude. By so doing, it will avoid the onus of an adverse public opinion, which will inevitably criticize it for indiscriminating action against an employee. It will preserve morale and avoid industrial conflict, by convincing labor of its genuine interest in the employee, rather than merely in his syphilis as an industrial hazard. It will avoid the cost of traumatic syphilis, and thus also the unfavorable position in which the employer is placed by existing workmen's compensation enactments.

Those interested in the epidemiologic attack on syphilis are concerned also to see industry assume an attitude of responsibility toward the prevention of the disease as a disease, quite as much as its control as an industrial hazard. If industry responds to this demand it will share the perplexities associated today with the interpretation of infectiousness. It will find that the disease is kept alive, so to speak, by a margin of infected persons who do not respond to so-called standard treatment procedures. It will find furthermore that there is as yet no satisfactory definition of the amount of treatment which will render any given patient non-infectious. On the other hand, as the best available practice, the systems proposed by the Coöperative Clinical Group and the U. S. Public Health Service for the standardized treatment of early syphilis, latent syphilis within the first 4 years, and even syphilis in pregnancy, should be familiar to every industrial physician. Already individual instances have been cited in which industrial concerns have refused the responsibility of seeing treatment through by an adequate standard, though they have insisted on, and, in fact, undertaken its initiation. The inadequacies of a policy which shift the responsibility for the treatment of syphilis in industry to the private general practitioner have been described in vigorous terms by such authors as Gehrman, who, in the case of the duPont interests, found inertia and unfamiliarity with modern methods among physi-

cians, to be one of the most serious problems with which it had to deal. The place given in Parran's statement of policy to educational activities and experiments in prophylaxis may be supplemented by the suggestion that an industry which is preventively-minded will concern itself with syphilis in the families of its employees, quite as much as with the disease in the employee himself.

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THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

NOVEMBER, 1938

ORIGINAL ARTICLES.

PROTEIN PRODUCTION AND EXCHANGE IN THE BODY
INCLUDING HEMOGLOBIN, PLASMA PROTEIN
AND CELL PROTEIN.*

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WHEN we consider the protein-building mechanism of the body it is logical to start with hemoglobin and plasma protein production under the stimulus of depletion. One may include also the building of new cells after injury during periods of zero protein intake and consider the exchange which may occur within the body as one protein contributes to the formation of another type of body protein. Reserve stores of protein-building material if present must be recognized and estimated before we can draw an accurate picture relative to new protein formation. One is impressed with the "fluidity" of the body protein reserve stores, which can very easily be moved from plasma to cell and *vice versa*, with little delay, with no detectable loss and without the anticipated catabolism to amino acids.

In this discussion of protein building within the body we must refer to *two types of standard animals*. A. The *standard anemic dog* has been rendered anemic by continuous blood withdrawal every week.^{37b} These dogs are maintained at a uniform anemia level of one-third normal or 40 to 50% hemoglobin (100% = 13.8 gm. hemoglobin per 100 cc.). A considerable reserve store of hemo-

* Twenty-first Mellon Lecture delivered before the Society for Biological Research of the School of Medicine, University of Pittsburgh, May 18, 1938.

globin-building material is removed during the first 6 to 8 weeks of continuous bleeding. At this level the dog is clinically normal in all respects and the hemoglobin removed each week to keep the anemia level constant represents the potency of the diet intake for that period. Such dogs are in effect testing machines by which can be measured the potency of a variety of food factors for hemoglobin production. *B.* The *standard plasma depleted dog* has been reduced to a state of hypoproteinemia^{30a} by daily plasmapheresis (a removal of blood followed promptly by a return of washed red cells suspended in a saline solution). The plasma-protein concentration of the blood is reduced from a normal of about 6% to the optimum experimental level of 4% and kept constantly at this level for weeks and months. This procedure presumably furnishes a stimulus for the production of new plasma protein. This 4% level is above the edema level of 3.5% and is well tolerated by the dog which remains active and clinically normal with a good appetite. After the *reserve store* is exhausted in 2 to 6 weeks, the plasma-protein production on a fixed basal diet is quite uniform. We can then study the effects of various procedures upon new plasma-protein production and can measure the potency of various proteins given in the diet as they influence new plasma-protein output.

Hemoglobin Production. It has been well established in standard anemic dogs³⁵ that the production of hemoglobin can be controlled by the diet intake. As a result of a long series of experiments food material has been measured as to its capacity to produce new hemoglobin under these standard conditions. We may divide foodstuffs into two groups—those favorable for hemoglobin production and those which are relatively inert. Livers^{31a} from warm-blooded animals head the list, and in the standard feedings (300 gm. liver per day for 2 weeks) effect a net output of approximately 100 gm. new hemoglobin. Among the foodstuffs favorable for hemoglobin production in the dog may be mentioned kidney, gizzard, spleen, pancreas and a few fruits—apricots, peaches and prunes. Muscle stands in an intermediate position and shows considerable variability in potency. In contrast, dairy products, fish and sea food, vegetables, grains and many fruits are relatively inert and contribute very little toward hemoglobin building under these conditions. Low-protein diets continued over long periods will cause a fall in the circulating hemoglobin.³⁴ Iron is the most potent inorganic factor.

Theoretically *amino acids* given in proper amounts and suitable mixtures should produce a calculated amount of new hemoglobin. At present, surely, we are far from that goal, but it can be shown that certain amino acids given with the basal diet will increase the production of new hemoglobin to about one-third the standard response to liver. Moreover, both the natural forms and optical isomers of histidine and phenylalanine are potent.^{37c} It has been

shown recently that one of the vitamins (riboflavin) has a definite influence upon the production of hemoglobin in these standard anemic dogs.⁷

Abnormal factors may modify new hemoglobin production in these standardized anemic dogs. *Infection* (endometritis) lasting over many weeks may completely inhibit the hemoglobin production in a standard anemic dog; but removal of the infected uterus will return the hemoglobin production to the normal level.^{31b} A sterile abscess will diminish temporarily hemoglobin production under standard conditions. The abscess will also abolish the hemoglobin production of the anemic dog during fasting periods in contrast to the control anemic dog which can produce abundant new hemoglobin during a 2 weeks' fast. Impaired intestinal absorption and significant blood destruction are excluded in these fasting experiments.^{31b} The evidence points to a disturbance of the internal metabolism related to hemoglobin building as responsible for this inhibition of hemoglobin production in such experiments.

A *bile fistula* also modifies new hemoglobin production in these standard anemic dogs. In fact, the output of hemoglobin is just about cut in half by a bile fistula and cannot be returned to normal by feeding large amounts of bile daily by mouth.⁸ It would appear that interruption of the normal flow of bile into the intestine changed the absorption of hemoglobin-building constituents. This is true for iron given by mouth, as the same dog can utilize iron with normal facility if it is given by vein. These bile fistula dogs can digest and absorb protein readily, as they maintain a constant weight, normal activity, appetite and general health. It would be hazardous to say that the bile fistula dog can digest and absorb protein for maintenance but not for hemoglobin building. We prefer to think of the bile fistula liver as somewhat disturbed and unable to take its full part in assembling the various constituents which go to the makeup of the mature hemoglobin as it appears in the erythrocyte.

Gastrectomized dogs^{13, 23, 25} produce less hemoglobin on standard diets in anemia than do normal dogs. It is not clear whether impaired digestion or some missing factor may be concerned.

Liver abnormalities in humans have been studied, usually relating to the missing constituents in pernicious anemia. Abnormal human livers have been tested in this laboratory³⁷ to show departures from normal in the content of hemoglobin-building material as tested in anemic dogs.

The investigator is always seeking to simplify biologic experiments and thereby exclude variables which are all too numerous in this type of experiment. *Fasting* presents some interesting reactions in these standard anemic dogs and these phenomena have received much study. During fasting periods of 2 to 3 weeks with the intake limited to sugar and water, the standard anemic dog will produce

considerable amounts of new hemoglobin (30 to 50 gm.). If this dog is fed a liberal amount of iron with the sugar the new hemoglobin production will average about 100 gm. As there is no protein intake the new hemoglobin obviously must be derived from body protein. This then is reducing the hemoglobin production to its simplest terms as regards food intake but this reaction can hardly be thus designated as it relates to internal protein metabolism. During this period of active hemoglobin production with zero protein intake, the *urinary nitrogen* shows a large decrease in its urea-ammonia fraction²—evidence that the nitrogenous precursors of the urea were retained within the body and presumably utilized for hemoglobin building. This has been termed the "reaction of conservation." In addition, there may be some exchange of protein materials within the body of the order of that described below.

Potency of Diet Factors for Hemoglobin Building in Anemia. Table 1 summarizes observations made on standardized anemic dogs fed designated amounts of potent food factors using the salmon-bread diet as the base line. The superiority of liver is obvious. The maximal and minimal figures in part represent differences in dogs, some animals being able to produce more new hemoglobin on a given diet than others. We cannot explain this fact but perhaps it is in harmony with the fact that some dogs can run faster or have more stamina than others.

TABLE 1.—HEMOGLOBIN POTENCY OF DIET FACTORS—AVERAGE VALUES

Diet factor daily intake.	Total net hemoglobin average output per 2 wks., gm.	Hemoglobin output per 2 wks.		No. of expts.
		Maximal, gm.	Minimal, gm.	
Pig liver 300 gm. . . .	93	124	69	77
Liver ext. 55 300 eq. . . .	56	72	37	22
Pig kidney 300 gm. . . .	69	92	49	9
Pig spleen 300 gm. . . .	82	100	55	3
Beef heart 300 gm. . . .	49	57	33	7
Apricots, dried 100 gm. . . .	42	92	13	31
Iron (Fe) 40 mg. . . .	53	95	25	43
Iron 400 mg. . . .	94	127	67	6
Salt mixt.—Fe 6 gm. . . .	9	22	0	16
Salmon bread 400 gm.	19	2	110

Plasma-protein Production. The *standard plasma depleted dog* by means of almost daily plasmapheresis can be brought to a steady state of hypoproteinemia and a uniform plasma-protein production on a uniform basal diet. We then are in a position to test the potency of diet factors which may influence the production of new plasma protein. Whole plasma (fresh or dried) heads the list²⁰ and it requires only 2.6 to 3.5 gm. of plasma protein by mouth to produce 1 gm. of new plasma protein in the depleted dog—a potency ration of 2.6 to 3.5. Various basal diets contain only 7 to 10 gm. of protein per day as fed and these small amounts of protein are well

utilized whether derived from grains, potato, kidney or liver. The potency ratios vary from 4.5 to 5.5. When larger amounts of liver are fed the potency ratio is 5.5 to 6.5, but in any case it requires at the maximum 6.5 gm. of liver protein as fed to produce 1 gm. of new plasma protein.

Other proteins are less successfully utilized—for example the proteins of red cells, beef heart, spleen and casein have potency ratios close to 10. In general, when larger amounts of protein are fed, the utilization is less efficient and the potency ratio rises. Plant and grain proteins²⁰ as a rule favor the production of globulin and cause a fall in the A/G (albumin-globulin) ratio which may even go far below 1. By contrast, the animal or visceral proteins favor a production of albumin and tend to cause a rise in the A/G ratio. Soy bean protein²⁰ is unusual and deserves a special note. It is very rapidly and completely utilized and favors albumin production (like animal protein) and has a potency ratio of 5 to 7.

Infection and intoxication¹⁸ disturb the plasma-protein production of these dogs and may check completely the new plasma-protein production. This includes cellulitis and sterile abscesses. Also intestinal disturbances will check plasma-protein production. Even the moderate intestinal disturbance due to fresh yeast feeding will check plasma-protein production, while autoclaved yeast is well digested and utilized to produce new plasma protein.

Fasting periods give interesting information.¹⁷ When the reserve store is depleted the dog can produce very little new plasma protein, 2 to 8 gm. per week. This means that the body cells can contribute but very little except the stored reserve protein to combat the dangers of hypoproteinemia; but as explained below the plasma protein can contribute advantageously and abundantly to the protein needs of the cells. This is in vivid contrast to the standard depleted anemic dog which in a week's fast can produce large amounts of new hemoglobin (50 gm.).

The regeneration of serum protein has been studied experimentally in the dog by Cowgill, Melnick and Burack.^{21,22} We believe their observations are in harmony with those reported from this laboratory. The interpretation of the experimental observations differs somewhat in the two laboratories.

Table 2 gives an interesting comparison of hemoglobin and plasma-protein production in depleted dogs. Liver alone is efficiently used to build new hemoglobin or plasma protein. Serum proteins and egg white are potent for plasma-protein building but less efficient for hemoglobin production. Casein, soy bean meal and salmon bread offer conspicuous contrasts. They are all used efficiently to produce new plasma protein but are ineffective in building new hemoglobin.

It should be emphasized that the *amounts fed* to the plasma depleted dogs are *less* than those fed to the anemic dogs. It is

certain that the depleted dog can produce very much more plasma protein than new hemoglobin and so much plasma protein can be produced that we cannot remove it fast enough—therefore the diet intake must be kept down. For this reason the + signs are added to the figures given in the plasma-protein production column (Table 2) indicating that the true total capacity is much above that listed. In general, the more protein fed, the more new hemoglobin or plasma protein is produced. The top limits are easily reached for hemoglobin production (75 gm. per week); but by this method the maxima cannot be established for plasma-protein production (100 gm.+ per week).

TABLE 2.—COMPARISON OF HEMOGLOBIN AND PLASMA PROTEIN PRODUCTION.

	Total net Hb. average output, 1 wk.	Ratio protein intake to Hb. output.	Total net plasma protein production 1 wk.	Ratio protein intake to plasma output.
Liver (pig)	50	8/1	65+	6/1
Serum (ox)	15	10/1	70+	3/1
Kidney (pig)	35	9/1	10+	7/1
Casein	14	42/1	45+	8/1
Heart (beef)	25	14/1	50+	10/1
Egg white	15	8/1	40+	5/1
Soy bean	5	35/1	20+	7/1
Salmon bread	7	50/1	50+	4/1

10 kilo dog, normal, 180 to 200 gm. hemoglobin in circulation.

10 kilo dog, anemic, 50 to 60 gm. hemoglobin in circulation.

10 kilo dog, normal, 30 to 35 gm. plasma protein in circulation.

10 kilo dog, plasma depleted, 20 to 25 gm. plasma protein in circulation.

Origin of Plasma Proteins. The *origin* of the blood plasma proteins has furnished material for debates among physiologists for years. It is now generally believed^{4,11,19,36} that one of the plasma proteins (fibrinogen) is derived only from the liver. Evidence is accumulating to indicate that the liver is actively concerned with production of the other plasma proteins. A large store of protein material is found in the liver,^{1,16} and it was shown many years ago^{14,32} that after a rapid and extreme plasma depletion the dog could throw into the circulating plasma considerable amounts of protein within an hour or two. Moreover, this reaction was abolished by the presence of an Eck fistula or severe liver injury.^{14b} More recently it has been observed¹⁵ that the Eck fistula modifies the capacity of the dog to maintain a normal concentration of plasma protein during periods of low-protein intake.

Observations related to clinical material cannot be reviewed carefully at this time. Much of this evidence has been reviewed by Peters, Van Slyke and associates in various papers²⁸ and texts.²⁹ They feel that there is some evidence that the plasma proteins are formed in the liver but much more evidence is needed and there are conflicting data. Another excellent review of hypoproteinemia in disease is that by Moschowitz.²⁴ Some workers¹² believe that the

reticulo-endothelium participates in the regeneration of plasma protein (globulin in particular).

Many authors,^{5,26} from a study of patients with liver diseases, conclude that the plasma albumin is produced in the liver. Chronic hypoproteinemia has been observed in many clinics^{27,33} sometimes associated with liver abnormality.

The plasma proteins may show very high levels in disease and this increase involves the globulin fraction.²⁸ This hyperproteinemia is common in myeloma⁶ and some other malignancies involving bone and in some inflammatory conditions³⁸ (lymphogranuloma, tuberculosis and syphilis). Under such conditions the *plasma-globulin fraction* may contain a miscellaneous assortment of protein materials derived from cell breakdown as well as the true plasma globulin and there is no certain proof as to how much, if any, the true plasma globulin may be increased under these conditions.

Reserve Stores of Protein-building Material. These reserve stores deserve attention in a general discussion of this type. We refer particularly to the stores of material from which the body can manufacture new hemoglobin or plasma or cell protein. These stores are probably largely in the form of proteins within cells (Fig. 1). These reserve stores may be reduced to low levels by fasting or a long period of low-protein diet or reduced practically to zero by long-continued anemia or by plasma depletion during periods of low-protein diet.

When these reserve stores of protein-building material are reduced to these low levels, the dog may react differently to certain types of intoxication—we may say that to a degree the reaction is conditioned by the presence of these reserve stores. One example is the reaction to a sterile abscess (Table 3). The normal dog when given a sterile abscess (1 cc. turpentine subcutaneously) promptly develops fever, leukocytosis and a sizable abscess lasting 3 to 5 days. Also there is great increase in urinary nitrogen to 2 to 3 times normal and this increase persists 6 to 8 days or longer. But the *depleted dog* shows little or *no increase* in the urinary nitrogen under identical conditions, although the abscess develops as usual with accompanying leukocytosis and fever. This has been observed in anemic dogs^{2b} and in plasma depleted dogs.¹⁸ It would appear that the *labile reserve protein stores* (Fig. 1) were concerned—that these stores are more susceptible to the systemic insult and intoxication of the abscess—that these proteins may break down more readily with release of toxic split products which are responsible for the general body protein injury and escape of the large excess of urinary nitrogen found in the normal undepleted dog. The observations recorded in Table 4 may fit in here. When larger amounts of plasma protein are given than the dog can metabolize, we may imagine these labile protein stores as piling up in large excess, so much so that this excess is broken down with the production of

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toxic split products which injure body cells and account for the great amounts of urinary nitrogen far in excess of the nitrogen in the protein given by vein. As this catabolism (Table 4) can be checked and controlled by increase of fat and carbohydrate by mouth, we may look at this reaction as similar to the tissue catabolism noted late in long fasting periods (pre-mortal rise)—the mechanism as a "protein sparing at the source."

TABLE 3.—URINARY NITROGEN INCREASED BY ABSCESSES.
Normal Dog 32-7.

	Nitrogen	Blood hemoglobin level %.
Before	0.8	19.5
After	1.2	18.5

TABLE 3.—URINARY NITROGEN INCREASED BY ABSCESSES.

Periods, 48 hrs.	Total N. mg.	Urea N + NH ₃ -N %	Creatin N, mg.	Uric acid N, mg.	Unde- termined N, %.	Weight, kg.	Blood hemo- globin level, %.
1	5,510	86.7	16	22	6.5	16.1	140 ±
2	10,740	89.1	228	52	3.8	15.3	
3	12,730	87.2	405	55	6.5		
4	11,460	85.8	278	54	8.7		
5	11,300	86.2	333	63	7.1	13.8	
6	11,180	85.7	386	49	8.0	13.4	
7	8,160	86.7	56	28	9.6		
8	6,470	86.7	14	18	9.6	12.6	
9	5,700	83.0	3	14	12.9		
10							

Figure 1 may help to visualize our concept of protein stores as they relate to the body cells and the circulating plasma protein. It indicates our belief that there can be an easy exchange between the plasma protein and the labile protein stores of the body cells. Another less readily available store of protein can be drawn upon by long periods of anemia, plasma depletion or protein fasting. The cell contains indispensable proteins which cannot be removed by any type of depletion. That body cells manufacture the body protein is a truism but we believe the liver cells are most concerned in the production of new plasma protein. The liver cells alone produce fibrinogen but the evidence is not yet convincing that

plasma albumin and globulin are also solely related to liver cell function. Strong evidence in favor of the production of plasma albumin by the liver is accumulating. We believe also that the liver is largely concerned with the production of the *globin* which makes up 95% of the finished hemoglobin as it appears in the mature red cell.

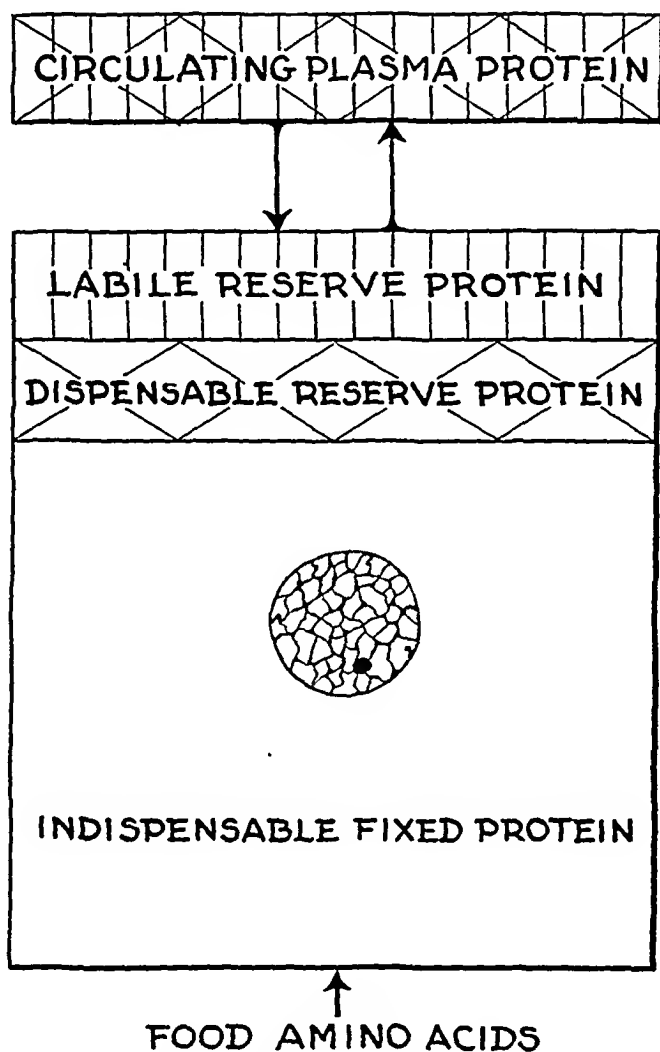


FIG. 1.—Protein stores within cells.

Exchange of Protein Materials Within the Body. Many illustrations come to mind as examples of the “fluidity” of protein reserves and the facility with which the body in times of stress can mobilize protein-building material. During a fast the depleted anemic dog can produce 30 to 50 gm. of new hemoglobin within a week. Also during a protein fast the dog can regenerate new liver cells to repair an extensive injury due to chloroform poisoning.³ During long depletion periods (anemia or plasma depletion) the dog draws out

all its reserve stores which presumably are within the body cells but when the depletion is discontinued the dog promptly repletes these stores and the repletion can be hastened by the injection intravenously of hemoglobin or plasma.

Plasma protein can contribute to the protein needs of the body cells and in fact the dog can be kept in nitrogen and weight equilibrium by means of intravenous plasma injections together with fat and carbohydrate by mouth. Many experiments touching this point have been published from this laboratory,^{2c,9,30b} but I wish to cite a single experiment (Table 4).

TABLE 4.—PLASMA INJECTION CAUSES INTOXICATION. CONTROLLED BY DIET.
Positive Nitrogen Balance.

Periods, 48 hrs.	Plasma injected, total N, gm.	Urinary total N, gm.	Urea N + NH ₄ -N, %.	Creatin N, mg.	Circu- lating plasma protein, gm. %.	Weight, kg.
1		8.73	89.4	129	7.1	15.9
2		7.58	92.0	96		
3		6.37	89.0	26		
4		6.04	89.2	26	...	14.5

Dog 34-146—Plasma Injection Begun—Sugar by Mouth—Intoxication.

5	3.66	11.11	88.4	221	7.0	14.4
6	3.59	10.39	90.0	146	7.7	
7	3.44	14.29	90.7	208	7.9	
8	3.37	17.49	88.9	340	8.3	13.0

Plasma Injection Plus Cowgill Diet—Positive Nitrogen Balance.

9	4.36	9.62	88.6	219	8.5	
10	4.11	2.89	68.8	28	7.7	
11	2.21	3.70	73.0	26	7.2	
12	4.12	3.47	71.9	13	7.5	13.3
13	4.42	2.61	64.5	16	7.9	
14	4.17	2.22	55.1	24	8.0	
15	2.14	2.01	56.8	14	7.6	13.2
16	4.24	2.34	58.2	21	8.2	
17	4.12	2.34	62.7	19	8.4	
18	2.02	2.36	63.3	10	8.5	

Plasma Injection Discontinued—Cowgill Diet Continued.

19		2.44	61.0	31	...	13.0
Period 1—fasting.						
Periods 2, 3, 4—given 50 gm. dextrose daily by mouth.						

The experiments in Table 4 are of the utmost simplicity but the reactions can hardly be so described. This normal dog^{2c} after 2 days of fasting was given water and sugar only, by mouth, for 6 days (Periods 2, 3, 4). Plasma obtained from normal donors was then given by vein, about 160 cc. each day. The amount of contained protein nitrogen is given in Table 4. It is obvious at a glance that the urinary nitrogen rises promptly to high levels—in Period 8 as high as 17.5 gm. This indicates some *intoxication* which is destroying body protein in excess of the plasma protein introduced. There is a conspicuous increase in creatine nitrogen which suggests

muscle protein injury. There was clinical evidence of intoxication as well.

When a protein-free diet (Cowgill) is given but the plasma injections continued, the dog drops promptly to low levels of urinary nitrogen, even below the expected levels on sugar intake alone. As the experiment continues the dog is maintained in a positive nitrogen balance (Periods 10 to 18—plasma-protein-nitrogen intake 31.5 gm. and urinary nitrogen output 23.9 gm.). There is even a slight gain in weight (Periods 8 to 16). Clinically the dog is normal during this period. The urea-ammonia fraction of the urinary nitrogen is very high (90%) during the period of intoxication but drops to low levels (55 to 60%) during the long period of positive nitrogen balance—"the reaction of protein conservation."

The recent experiments of Howland and Hawkins¹⁰ show that this plasma-protein utilization can go on actively in the phlorizinized dog without the appearance of any excess sugar or nitrogen in the urine, indicating utilization without any extensive catabolism of plasma protein as in digestion. This suggests a cleavage into large aggregates which are promptly combined to supply the special protein requirements of the specific body cells.

These observed facts invite speculation concerning involved mechanisms. For plasma protein to be stored or utilized in the liver, muscles or body tissues, it must be stored at such or slightly catabolized (large aggregates rather than amino acids) and re-synthesized to cell protein. This mechanism may be disturbed by overloading (injection of too much plasma) or lack of adequate carbohydrate and fat. As a result the catabolism may get out of hand and within or without the body cells produce toxic split products with consequent intoxication and a large surplus of urinary nitrogen much above that contained in the introduced protein.

The diagram (Fig. 2) may help to visualize reactions which relate to much data reviewed above. Food through amino acids contributes to the cell proteins of liver, muscle and body tissues. The liver cell (and its protein) contributes directly to plasma protein and hemoglobin. There is an important *protein exchange* (fluidity) which may go on *within the body* and concerns many of the reactions described above. The plasma protein may contribute *easily* to body protein needs (muscle, liver and hemoglobin), but these other tissues can contribute only with difficulty to plasma protein by this method of exchange (after the reserve stores are depleted). Other tissues contribute easily to hemoglobin (for example, in fasting), but hemoglobin can contribute less readily, if at all, to other body proteins. This type of exchange does not concern profound cleavage and amino acids, but we think of it as related to a slight cleavage of proteins into *large aggregates* which can readily be assembled to form the protein of the special cell or the reserve store related to that cell.

It is probable that these *large aggregates* have to do with *intracellular* reactions in the main. For example, the rapid exchange back and forth between the plasma protein and body cells would seem to call for slight modification of this labile reserve protein which could hardly occur except within the cell.

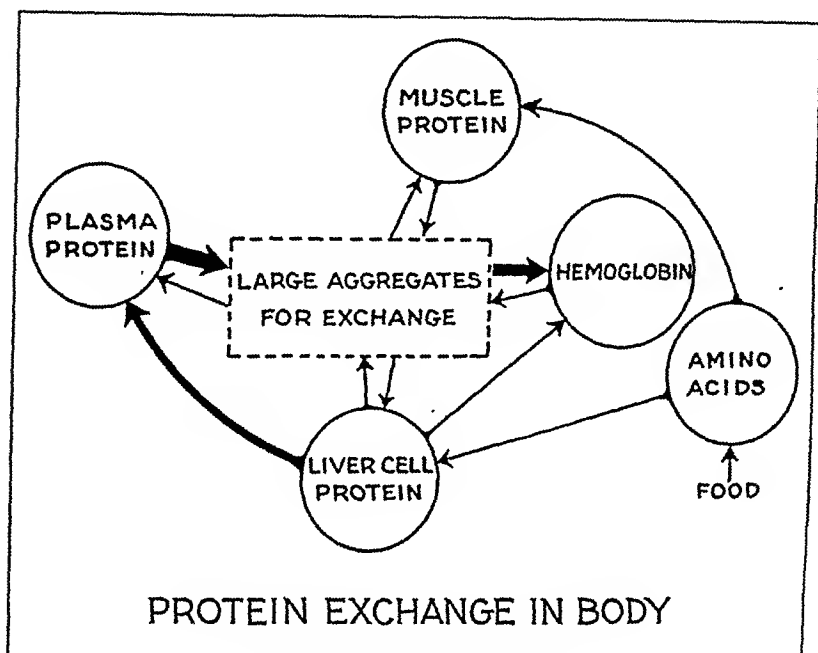


FIG. 2.—Protein give and take.

All of these experiments point to the *liver* as of primary importance in body protein metabolism. We believe it is proper to think of the liver as participating in the assembly of amino acids and other constituents of body proteins into aggregates which may be used in the liver or elsewhere to form the specific protein of the body cell. Whether we think of protein exchange in the body, or of protein reserve stores or of protein fabrication, we may well give first place to the liver as the agent, bank or factory.

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LEUKOPENIC LEUKEMIA OF THE MYELOBLASTIC TYPE.

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MYELOBLASTIC leukemia is usually regarded as a type of the acute leukemias. Acute or blastic leukemias, as a rule, run comparatively short courses, and frequently enlargement of lymph nodes, spleen and liver is encountered at some time during the disease. Increase in number of the leukocytes because of immature or embryonic cells is usual in this group of leukemias. There also may be present purpuric manifestations and ulceration of mucous membranes. Forkner¹ has given a good account of the differential diagnosis of the three types which are most commonly found.

Reports of cases of blastic leukemia which have shown little purpura, frequent leukopenia, and absence of clinical enlargement of spleen, liver or lymph nodes are rather rare. Such cases as have been reported also have tended to be subacute rather than acute in

nature. Hirschfeld,² Pinkerton,⁶ Weber,⁷ Kracke and Garver,⁴ and Mettler and Purviance⁵ have reported in all a total of 13 cases in which the clinical pictures had many similarities. In the case of Hirschfeld and in those of Pinkerton the cell type is difficult to make out. The case of Kracke and Garver was not followed but was probably lymphoid, while the one reported by Weber and those of Mettler and Purviance were myeloblastic in type.

It is probable that certain others have been reported, and misdiagnosed as aplastic anemia. It is also possible that some authors have termed this type of disease aleukemic leukemia, but, as Jaffe³ has pointed out, that term should be reserved for leukemia with a normal blood picture.

In this communication we are reporting 5 cases which have many points in common with the former group. All were studied in Lakeside Hospital in the past 3 years. We believe that each of these was myeloblastic in type, not only because of the type of cells found in preparations stained with Wright's stain but also because of the appearance of the abnormal cells with supravital stains. To strengthen this point, in 3 of the cases peroxidase reaction gave a high percentage of peroxidase positive cells.

Case Abstracts. CASE 1.—M. H., a 37-year-old white woman, who entered the hospital for the first time on January 28, 1935, complaining of pain in the left thigh, weakness, and fever.

About 4 years earlier she had had the cutaneous manifestations of purpura. She was found to be sensitive to oranges, and the purpura disappeared following the elimination of oranges from her diet. For 5 months prior to entry she felt below par, and her physician found her to be anemic. Iron therapy did not alleviate her symptoms. Nine days before admission she noticed the beginning of a painful swelling in the lower posterior surface of her left thigh, accompanied by chilly sensations and a fever which, at times, reached 39.3° C. She was then sent into the hospital.

Physical examination revealed a well-developed, well-nourished woman of 37 years. Temperature on admission was 39.2° C., pulse 120, respirations 28, blood pressure 130/80. Relevant findings on physical examination were as follows: There were two small purpuric spots present, one on the right hand and one on the left leg. The mucous membranes were pale; no petechiæ were seen. There was a tender indurated area on the posterior aspect of the left thigh, about 10 cm. proximal to the knee joint. No lymph nodes were palpable; the spleen and liver could not be felt.

Laboratory Findings on Admission: Urine: hazy, acid, specific gravity 1.018, albumin—slightest possible trace, sugar negative, sediment essentially negative; blood: erythrocytes, 2,340,000, hemoglobin, 53% (Sahli), leukocytes 7450. Differential showed 12% neutrophils, 37% lymphocytes, 41% blast cells, and 10% unclassifiable. Peroxidase stain showed 60% granular and 40% non-granular cells. The red blood cells in the smear were large, and the number of platelets was greatly reduced. Blood culture was negative. Icteric index was 12. Blood sugar was 84 mg.%. Blood urea nitrogen 8 mg.%, blood uric acid 3.8 mg.%, blood calcium 9.1 mg.% and cholesterol 92 mg.%.

Hospital Course: For the first 27 days of her hospitalization temperature varied between 38° C. and 41° C. Seven days after admission several petechiæ were noted in the mouth and throat, and several small, dirty gray

ulcers of the pharynx were noted. At this time the leukocyte count was 23,350 with 19% neutrophils, 5% lymphocytes, 4% myelocytes, 67% blasts, and 5% unclassifiable cells. Nucleated red cells were seen in the smear. Thus far one blood transfusion was given, then 6 more were given. Roentgenograms of the chest and abdomen were essentially negative. The patient continued febrile, as noted, and on the 14th hospital day developed pleuritic pain in the right chest and a friction rub. On the 25th hospital day a large quantity of mucopurulent material was obtained from the thigh, containing by culture *S. aureus hemolyticus*. Following this, improvement was progressive, temperature dropping to normal and remaining normal until her discharge on the 61st hospital day.

The variation in blood counts is interesting. In 52 complete counts the lowest leukocyte count recorded is one of 1400 with 33% neutrophils, 64% lymphocytes, 2% monocytes, and 1% eosinophils. The highest count was one of 29,300 with a differential of 58% neutrophils, 9% lymphocytes, 3% monocytes, 10% myelocytes, and 20% blasts. Before incision of the thigh abscess the leukocyte counts were in the 20,000 range, always having a variable number of blast cells; after the drainage was instituted the count immediately dropped to 5000 and less, with differential counts nearly normal, with the exception of slight depression of neutrophils, and an occasional blast cell. In addition, erythrocyte count and hemoglobin rose and remained up following incision and drainage of the abscess, and at discharge were nearly normal with a normal number of platelets. At no time were lymph nodes, spleen or liver palpable.

The patient remained at home for 5 months, feeling quite well. She had a few purpuric spots occasionally, and her leukocyte count varied between 1900 and 4000, the differential showing 2 to 16% neutrophils and 0 to 28% blast cells. The erythrocyte count and hemoglobin then began to drop and she became weaker. She reentered the hospital on September 15, 1935, for transfusion (500 cc. of citrated blood). No lymph nodes were palpable, nor could the spleen or liver be felt. Four days following this many tender, circumscribed, non-fluctuating areas from 1 to 4 cm. in diameter appeared over her arms, shoulders, and chest. After another transfusion, the lesions cleared rapidly and she was discharged. At home, she was given increasing doses of Fowler's solution, as her leukocyte count was around 12,000 with 67% blast cells. Fowler's solution was discontinued because of toxic symptoms, and because the type of cell in the smears did not change nor did the count become reduced. She had been rehospitalized meanwhile, and 5900 cc. of citrated blood was given during her stay in the hospital. She remained in the hospital 86 days, and the leukocyte count remained below 4000 with a high percentage of blast cells except for a few occasions when the total count rose to around 10,000. A sternal marrow biopsy was done and histologic examination showed that the marrow spaces were completely occupied by medium-sized cells with large nuclei, believed to be blastic in type, and almost complete absence of erythrocyte formation (Fig. 1).

She was discharged from the hospital on January 10, 1936, and readmitted on January 23, 1936, with a sore mouth. She remained in the hospital until her death 77 days later. During this time she developed abscesses in the right axilla and in the left lumbar region. From the axillary abscess *S. aureus hemolyticus* was cultured and from this a vaccine was made. Her mouth became progressively worse, she gradually lost weight and strength, and finally went into circulatory collapse and died.

During the last month of her hospital stay she was given increasing doses of the autogenous Staph. vaccine, starting with 0.05 cc. (1.0 cc. = 1 billion organisms) and increasing to 1.5 cc., but this only after she had received 20,000 units of Staph. antitoxin. The day after each injection of this vaccine her leukocyte count rose to a new high level and the next day again

dropped, but not to the previous level. The vaccine was started when the leukocyte count was 15,000 of which 50% were blast cells and after the last injection it was 117,000 of which 90% were blast cells. The last injection was given 5 days before death and the day before death her count had returned to 50,000. Liver, spleen, and lymph nodes were not palpable at the time of death.

Autopsy (by Dr. Howard Jackson, April 9, 1936). *Pathologic diagnosis* included: Myeloid leukemia, leukemic hyperplasia of sternal and vertebral marrow, purpura, and bronchopneumonia.

Liver weighed 2150 gm. It was smooth, firm, and sharp-edged. The cut surface showed the usual lobular pattern. Histologic examination showed normal architecture, with no evidence of leukemic infiltration. The *spleen* weighed 400 gm. Histologic examination revealed no abnormal cells. No enlarged *lymph nodes* were found. Sections were made from nodes from axillary, cervical, mediastinal, and abdominal regions, all showing normal lymph node architecture with no abnormal cells.

Bone marrow (sternum, ribs, and vertebræ): Grossly, the vertebræ and sternum contained abundant, viscid, pale pink marrow, which on histologic examination showed striking lack of maturation of the leukocytes. The majority of leukocyte elements were immature; some were large round cells containing large round vesicular nuclei, while some contained basophilic and acidophilic granules in the cytoplasm. Some large round cells were noted, also, containing large round dark-staining nuclei and clear cytoplasm. Very little evidence of erythropoiesis was seen.

With Wright's stain, the majority of cells were large, with clear blue cytoplasm and large round nuclei containing nucleoli; the greatest number of these were myeloblasts.

Comment on Case 1. The points of interest in this case are: 1, the duration of the disease, which was about 20 months; 2, the apparent remission of 5 months during which time the patient seemed completely well, except for a continued low leukocyte count.

Attention should also be called to the rise of leukocyte count to 117,000. This apparently was concomitant with the use of autogenous Staph. vaccine. The drop to 50,000 occurred when the vaccine was discontinued.

In the long period during which we observed this patient numerous blood studies were made. Auer bodies were frequently found in the blast cells stained with Wright's stain; these same bodies could be made out easily as neutral staining rods when neutral red was used in supravital preparations of the blood. With the supravital preparation a more progressive link between the youngest and oldest cells could be described. Bone-marrow biopsy and autopsy both confirmed the diagnosis of myeloblastic leukemia in this case.

CASE 2.—D. F., a 21-year-old white man, was referred to the hospital on September 2, 1936, by Dr. J. M. Painter of Kent, Ohio, complaining of pallor, weakness, and dyspnea on exertion.

His illness had started 5 months previously, when he began to suffer from anorexia. Two months before admission he became weak and pallid, and began to lose weight. There were dyspnea and palpitation on exertion, and slight parasthesia of the extremities. Past history was unimportant, except for the fact that he had worked with arsenical insecticides for 1 month about 9 months prior to admission.

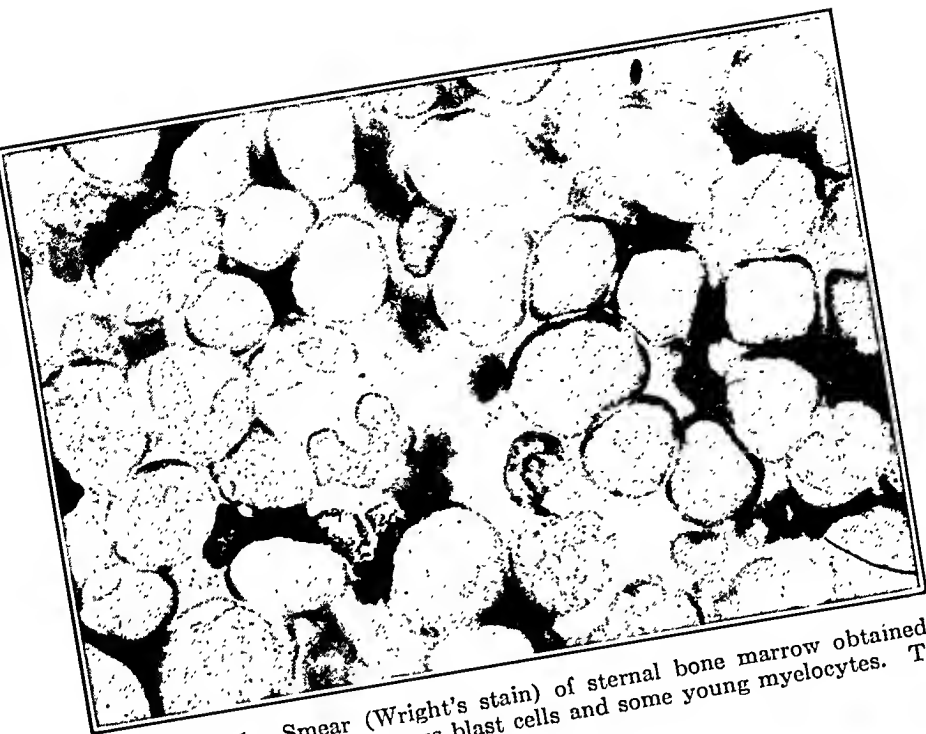


FIG. 1.—Case 1.—Smear (Wright's stain) of sternal bone marrow obtained by biopsy ($\times 900$), showing numerous blast cells and some young myelocytes. There is almost complete absence of erythropoiesis.

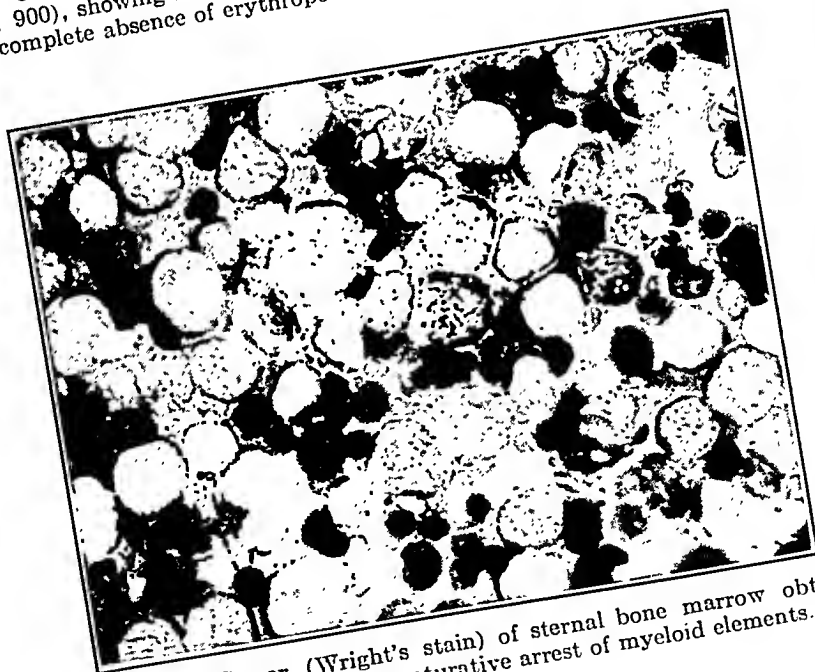


FIG. 2.—Case 2.—Smear (Wright's stain) of sternal bone marrow obtained by biopsy ($\times 700$), showing maturative arrest of myeloid elements.

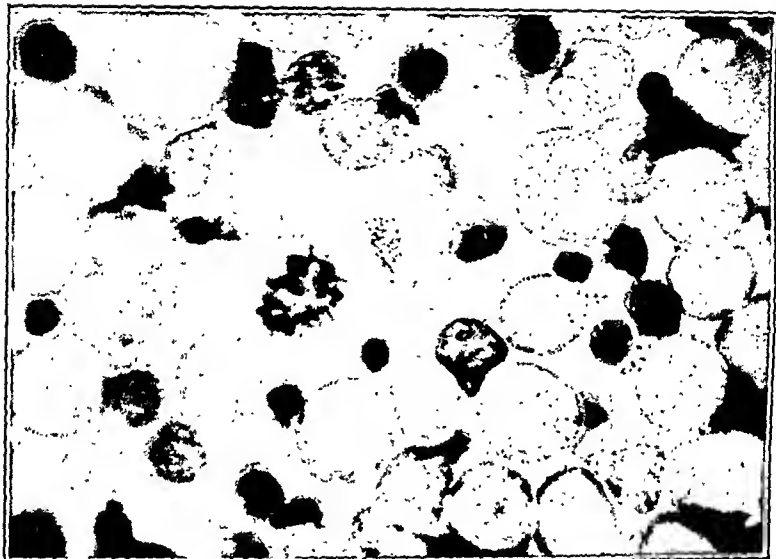


FIG. 3.—Case 3.—Smear (Wright's stain) of sternal bone marrow obtained by biopsy ($\times 900$), showing marked nonmaturation of white cell elements, but not to the extent found in the marrow of Case 1. Erythropoiesis is still active.

Physical examination revealed a pallid, poorly nourished, young man of 21. Temperature was 37.5° C., pulse was 96, respirations 22, and blood pressure 110/80. Relevant points on physical examination were: A few small petechiæ were seen in the skin and mucous membranes, and a small abscess was noted on the right external ear. There was no enlargement of the lymph nodes in any region. Spleen and liver were not palpable.

Laboratory Findings: Urines were negative for albumin and sugar. Kline exclusion test was negative. Blood chemistry showed values all within normal limits. Bleeding time was 4 minutes and 15 seconds; clotting time about 2½ minutes. Icteric index was 7. Cell fragility was normal. Gastric analysis showed 30° free hydrochloric acid after histamine. All blood cultures were negative. *S. aureus hemolyticus* was cultured from the auricular abscess.

The blood, on admission: erythrocytes, 1,300,000; hemoglobin, 35%; leukocytes, 5100. Differential: 65% neutrophils, 25% lymphocytes, 2% monocytes, 2% myelocytes, and 6% blasts. There were 18 nucleated erythrocytes per 100 leukocytes counted. The blast cells were determined to be myeloblasts by the use of supravital technique.

Course: The patient was mildly febrile. Small numbers of petechiæ appeared frequently in the skin and mucous membranes. One blood transfusion of 500 cc. was given, and a biopsy of the sternum was performed. This showed hyperplasia of the white cell elements and some mitoses. The young red cells were reduced in number and there was also nonmaturation of all cell elements. The megakaryocytes were reduced in number (Fig. 2).

The patient remained in the hospital only 6 days. No enlargement of liver, spleen or lymph nodes was discernible at any time. Leukocyte counts varied from 2400 to 5750, and as high as 12% blast cells were seen in some of the smears. At discharge, October 6, erythrocyte count was 1,530,000 and hemoglobin was 50%.

Follow Up: He was given two more transfusions. On Nov. 20, 1936, he began to develop edema of his legs, his erythrocyte count was 1,400,000, hemoglobin 35%, and leukocyte count 18,000. The type of cell remained unchanged. He developed marked edema and ascites which was relieved somewhat with salyrgan. The last blood counts on Jan. 19, 1937, showed 1,860,000 erythrocytes, 40% hemoglobin, and 40,000 leukocytes. He died Jan. 23, 1937. No autopsy obtained.

Comment on Case 2. The diagnosis of myeloblastic leukemia was made in this case not only from the blood cells but from the hyperplastic state of the bone marrow and the number of immature cells present in that organ. The course was shorter than any other of our cases but this might be accounted for by the smaller number of transfusions which were given.

CASE 3.—R. C., a 23-year-old white man, was admitted to the hospital on April 20, 1936, complaining of dyspnea of 5 months' duration.

Past history revealed that he had sold gasoline, including the ethyl type, for 5 months in 1934, and for 5 months early in 1935 had worked in enamel dusts said to have contained lead.

Five months previous to his admission he began to experience dyspnea on exertion and palpitation; accompanying this were a slight non-productive cough and weight loss. For the 8 weeks prior to admission he had noticed pallor, and his gums had bled easily. Two weeks before admission a moderate epistaxis occurred. A physician was consulted and parenteral liver was given; the patient continued to feel weak, and hospitalization was advised.

Physical examination revealed a well-developed, well-nourished, white man lying quietly in bed. Temperature was 38.5° C., pulse 120, respira-

tions 24, and blood pressure 120/50. The skin was very slightly icteric; a few petechiæ were noted over the anterior chest wall. Tongue was pale but not atrophic; the gums bled easily, teeth were carious and dirty. The heart was slightly enlarged to the left, with a gallop rhythm at the apex, and a systolic murmur over the entire precordium. There were no lymph nodes palpable anywhere, and the liver and spleen could not be felt.

Laboratory findings on admission: urine, negative; Kline exclusion test, negative; icteric index was 18; gastric analysis: 60° free hydrochloric acid after histamine; fragility test was normal; many stools intermittently benzidine positive.

Blood counts: erythrocytes 1,070,000, hemoglobin 25%, leukocytes 7700; differential: 63% neutrophils, 28% lymphocytes, 9% monocytes, and almost no platelets. There was a 5% reticulocyte count.

Course: Three weeks after admission a sternal biopsy was done. The marrow was markedly hyperplastic in all elements except megakaryocytes. There were many young myelocytes, and increased numbers of myeloblasts. Increased mitotic figures were seen both in red and white cell elements. Auer bodies were seen in a few cells (Fig. 3).

During the first 70 days the patient's course was febrile. The only effective therapeutic agent was blood transfusion. The patient received a total of 5000 cc. of blood during this hospital stay. He improved considerably, but on Aug. 14, 1936, he was found to have a total leukocyte count of 2550 with 42% neutrophils, 46% lymphocytes, 4% myelocytes, and 8% blast cells. He was discharged on the 106th hospital day, afebrile and feeling much better.

Patient remained at home for 3 weeks, during which time he lost strength and became dyspneic, and began to have severe headache accompanied by stiffness of the neck. He was readmitted on Sept. 3, 1936. At this time physical examination was similar to his previous examination, but the spleen was thought to be palpable at the costal margin. Temperature was 38.5° C.

Laboratory Findings: Urines were negative. Lumbar puncture showed an initial pressure of 230 mm. spinal fluid, but examination of the fluid was negative. Blood: erythrocytes 2,430,000; hemoglobin 60%; leukocytes 13,300; differential: 52% neutrophils, 14% lymphocytes, 2% monocytes, 6% myelocytes, and 26% blast cells. Twenty-seven nucleated erythrocytes were seen per 100 leukocytes counted. At this time there were over 60% granular cells in the blood smear as shown by peroxidase reaction.

Following admission the leukocyte count dropped to 5000 and remained low for some time. The patient developed abscesses of the gluteal region and one finger, which were incised and drained. Material from the abscesses was cultured and from this was grown *S. aureus hemolyticus*. Thirty-eight blood transfusions were given. Staph. toxoid was given in increasing doses over two periods of time in an effort to increase his resistance to infection. The leukocyte count continued low with a large number of blast cells, except for one period of 12 days which corresponded to the use of the largest doses of Staph. toxoid when it reached a peak of 75,000 with 44% neutrophils, 10% lymphocytes, 9% myelocytes and 35% myeloblasts. Supravital studies again showed more of a link between the blast cells and the mature ones than did the Wright's stain. Following this it dropped to an average of 5000. Decubiti appeared, the patient became progressively weaker, and death occurred on the 126th hospital day. At the time of death the spleen was barely palpable, and no enlargement of liver or lymph nodes was present.

Autopsy (by Dr. W. B. Wartman, Jan. 3, 1937). Examination of the skin at the time of autopsy revealed a few small scattered petechiæ, and numerous decubiti of the back and buttocks.

Examination of the lungs showed numerous small communicating abscesses of both upper lobes. Histologic section of these areas showed extensive infiltration with a cellular exudate comprised principally of mononuclear cells having a clear pink cytoplasm and round chromatic nuclei containing nucleoli (hematoxylin and eosin stain). In the remaining sections of the lung normal architecture was preserved.

The spleen weighed 475 gm., and grossly the architecture was normal. Histologic section showed normal splenic architecture, altered somewhat by infiltration by masses of mononuclear cells similar to those seen in the areas surrounding the abscesses in the lungs.

The only significant enlarged lymph nodes were those of the abdominal paravertebral chain, these nodes averaging 2 by 1 by 0.5 cm. Sections of these showed well preserved architecture, but fairly extensive infiltration with the mononuclear cells described above.

The bone marrow of vertebræ, sternum, and ribs showed considerable increase in cellularity, due to the replacement of normal elements by the mononuclear cells described above. No megakaryocytes or megaloblasts were present, but erythrocytes and nucleated red cells were present in normal numbers.

No other infiltrations with mononuclear cells were seen elsewhere.

Comment on Case 3. The points of interest in this case are similar to those in Case 1: 1, The duration of the disease was 12 months; 2, although there was no definite remission as was described in the first case, the patient did improve for a time and left the hospital in fair condition and remained at home 3 weeks following numerous transfusions and supportive therapy. Again in this case we wish to call attention to the stimulated rise of the leukocyte count from about 6000 to 75,000 following injection of Staph. toxoid, and the subsequent fall to leukopenic levels after the toxoid injections were discontinued. A rise in leukocyte count was not elicited with diphtheria toxoid nor was a second rise of it elicited when Staph. toxoid was again given. In either case this might be explained by insufficient dosage.

CASE 4.—A. S., a 60-year-old white man, admitted to the hospital on Jan. 18, 1937, complaining of weakness. For 3 years previous to his admission he had had intermittent epigastric distress and moderate indigestion. In the 6 months previous to his admission he had become progressively weak and lethargic. A physician discovered that he had a hemoglobin of 55%, and he was hospitalized for study.

Physical examination revealed a well-developed and well-nourished, white man lying quietly in bed. Temperature was 37° C., pulse 88, respirations 20, blood pressure 108/60. The skin and mucous membranes were pale. There was a sinus behind the right auricle, communicating with the middle ear, which had been present for 33 years following mastoidectomy. No petechiæ were noted in the mucous membranes. There was no enlargement of the lymph nodes. Physical examination was otherwise entirely normal.

Laboratory Findings: Urines were essentially negative. Gastric analysis showed 48° free hydrochloric acid following histamine. Icteric index was 6. Blood chemistry was within normal limits. Stools showed intermittently positive benzidine tests.

Blood: Erythrocyte count 2,390,000, hemoglobin 42%, leukocytes 2600. Differential: 24% neutrophils, 52% lymphocytes, 1% eosinophils, 23% blast cells, and 10 nucleated erythrocytes per 100 leukocytes. Peroxidase

reaction done at this time showed that many of the earliest cells contained a few granules.

Course: He was given 3 blood transfusions of 500 cc. each, and improved considerably during his stay. The total leukocyte count never rose above 4200, the highest number of blast cells being 29%.

Following this discharge the patient was hospitalized on 7 occasions for blood transfusion. In all, he received a total of 21 transfusions of 500 cc. each. This maintained his erythrocyte count between 2,500,000 and 3,500,000. At the end of May, 1937, the spleen could not be felt, nor had the liver or lymph nodes been palpable at any time. During this entire time the leukocyte count averaged 5000 cells with a high percentage of blast cells, and on two occasions reached 11,000. On two occasions he had scattered petechiæ on both legs, and for 2 or 3 weeks his gums bled easily.

On June 30, 1937, the patient suddenly developed pain in the right lower chest, accompanied by a cough productive of purulent bloody sputum. Examination revealed consolidation of the right middle and lower lobes of the lung. He was admitted to the hospital immediately with a temperature of 40.7° C., went downhill very rapidly, and died 14 hours after onset of the acute episode. No autopsy was obtained.

Comment on Case 4. This case was of interest because the patient remained in excellent condition throughout his illness. The only thing that incapacitated him was his anemia. He maintained his weight throughout his illness, and he was up and about, living a fairly normal life until within 15 hours of his death. His leukocyte count was never over 15,000, platelets at all times were low.

In this case again the diagnosis seemed to be assured by the absence of involvement clinically of other organs than the bone marrow, as well as the classification of the abnormal cells by the means of Wright's stain, supravital dyes, and the peroxidase reaction.

CASE 5.—J. S., a 69-year-old white man, was admitted on March 25, 1937, with a complaint of weakness. During the 6 months prior to his admission the patient had been losing weight. Associated with the weight loss there was some dyspnea and pain in the right leg. He was given many parenteral doses of liver extract and 3 blood transfusions, and was finally referred to the hospital.

Physical examination showed a well-developed, poorly nourished, white man lying quietly in bed. Temperature was 38° C., pulse 100, respiration 22, blood pressure 110/50. There was slight dyspnea. Skin was pasty; no petechiæ were noted. There was slight cyanosis of the nails. The chest wall was rigid, and a few moist râles were heard at both bases. The heart was slightly enlarged; no murmurs were heard. Liver and spleen could not be felt; there were no palpable lymph nodes. Pitting edema of both ankles was present.

Laboratory Findings: Urines were not remarkable except for a small amount of albumin. Gastric analysis showed free hydrochloric acid after histamine. Icteric index was 4; blood chemistry was within normal limits; stools gave occasional positive tests for occult blood.

Blood: Erythrocytes, 1,860,000; hemoglobin, 32%, leukocytes 1300. Differential: 28% neutrophils, 60% lymphocytes, 4% monocytes, 5% myelocytes, and 3% unclassified cells.

Course: The patient was digitalized upon admission, with subsidence of edema and dyspnea. Six transfusions of 500 cc. each were given, with a rise in erythrocyte count and hemoglobin. Two days after admission blast cells were first seen in the smears, and continued to be seen until discharge.

The leukocyte count during his entire stay (36 days) never rose above 2750, and the percentage of blasts never rose above 6. He was discharged from the hospital feeling much better on May 1, 1937.

The patient was readmitted 3 weeks later because he had been feeling poorly. Two transfusions of 500 cc. each were given, and he was discharged. Blood counts remained about the same.

He was again admitted on June 9, 1937, for transfusion. Leukocyte counts were unchanged, but at this time both spleen and liver were just palpable. He was given 11 transfusions. However, his course was progressively downhill, and he finally went into circulatory collapse and died. Final leukocyte counts remained low, but the percentage of blast cells had risen to 27 at death. At the time of death both liver and spleen were moderately enlarged.

Autopsy (by Dr. M. A. Simon, Aug. 17, 1937). The only notable point on examination after opening the body was enlargement of the liver and spleen. The liver weighed 2450 gm., and gross examination of the cut surface revealed no abnormality. Histologic section showed hyperemia and dilatation of veins and sinusoids, but no abnormal infiltrations. The spleen weighed 740 gm., and cut section showed some obscuring of the Malpighian corpuscles. Histologic section showed normal architecture, but the splenic pulp contained innumerable white cells in all stages of development, being a striking picture of extramedullary hematopoiesis. The most striking form seen was a large multinucleated form resembling an atypical megakaryocyte.

No enlargement of lymph nodes was found, but in one node a small area similar to the picture seen in the spleen was found.

Bone marrow of sternum, ribs, and vertebrae was watery and pale red, definitely not pyoid in character. The sections showed the same changes noted in the spleen. Every stage of development of both red and white cell series was seen, with giant multinucleated cells resembling megakaryocytes.

No other leukemic changes were found anywhere.

Comment on Case 5. This case was admitted with a diagnosis of aplastic anemia. At no time until nearly the day of death did he show sufficient abnormal cells to make differentiation with peroxidase reaction necessary. From time to time supravital stains were employed but to no advantage. It seemed to us throughout the course of the disease that the greatest damage lay in the bone marrow and this was confirmed at autopsy, although the spleen contained extramedullary hematopoiesis.

Discussion. In all, we give 5 cases of leukemia each of which was myeloblastic. As pointed out earlier, blastic leukemia of the myeloid type is usually regarded as an acute disease; and also, as a rule, has infiltration if not metastases of the myeloid elements into many organs. In only 1 of the 3 autopsies obtained was there no infiltration in the spleen. Throughout the clinical course of all 5, only in the 2 cases showing splenic infiltration at autopsy was there any clinical indication of other than bone-marrow change. Even in these cases there never were enlarged lymph nodes and in these cases the spleen was only moderately enlarged.

The clinical course of each of these cases is longer than that of the average myeloblastic leukemia, and their average course is longer than the average of the 13 cases referred to earlier. In each case

TABLE 1.—ANALYSIS OF 13 CASES FROM THE LITERATURE AND OF OUR 5 CASES.

No.	Author.	Age (yrs.).	Sex.	Chief complaints.	Physical findings.				Fever.	Bleeding from gums.	Early leukocyte picture.						Platelets.	Final leukocyte picture.						WBC at death (discharge).	Neutrophils.	Lymphocytes.	Monocytes.	Eosinophils.	Basophils.	Myelocytes.	Myeloblasts.	Nucleated RBC.	Lowest WBC.	Highest WBC.	Duration of disease (months).
					Petechie.	Lymph nodes.	Liver.	Spleen.			RBC at onset.	WBC.	Neutrophils.	Lymphocytes.	Monocytes.	Eosinophils.		Basophils.	Myelocytes.	Myeloblasts.	Nucleated RBC.	WBC at death.	RBC at death.												
1	Hirschfeld, 1914	38 M		Pallor	Weakness	+	+	0	0	1.50	1.12	20,000	12	73	15	?	2,000	2,000	20,000	7			
2	Finkerton, 1929	52 M		Pains in arms, legs, joints	Weakness	+	+	0	Pal- pable	3.12	1.16	6,500	4 to 6	Occa- sional	?	3,900	3,900	6,500	7				
3	Finkerton, 1929	61 M		Pallor	Weakness	+	+	0	Pal- pable	3.00	1.50	2,500	?	2,100	2,100	2,500	10				
4	Finkerton, 1929	58 F		Fever	Weakness	+	+	0	Pal- pable	3.12	1.16	2,100	8	80	0	Rare	1,500	1,500	2,100	2				
5	Finkerton, 1929	16 F		Weakness	Epistaxis	+	+	Small axillary and inguinal	En- larged	1.64	1.12	3,150	35	48	Few	?	1,200	1,200	3,450	4				
6	Finkerton, 1929	3 M		Pallor	Weakness	+	+	0	0	1.09	?	5,500	21	79	0	Greatly reduced	9,950	34	22	0	0	10	31	0	2,700	11,400	9					
7	Weber, 1932	31 M		Pallor	Weakness	+	+	0	0	0.77	1.75	3,900	22	48	6	0	6	18	0	700	700	1,100					
8	Kraeke and Garver, 1935	47 M		Anemia	Weakness	+	+	0	0	1.10	1.00	1,100	Predominantly small lymphocytes; occasional leukoblast.	1,350	41	25	1	4	0	18	2	1,350	7,600	10						
9	Metzger and Vance, 1937	21 F		Menorrhagia	Weakness	+	+	0	0	4.31	?	7,600	41	45	3	0	4	5	1	950	36	16	12	0	20	16	0	950	2,450	12					
10	Metzger and Vance, 1937	38 M		Weakness	Pallor	+	+	0	0	3.27	0.50	2,300	29	42	20	0	1	0	2	5,000	40	32	2	0	2	14	60	5,000	5,300	41					
11	Metzger and Vance, 1937	47 M		Weakness	Dyspnea	+	+	0	0	0.87	1.08	5,300	44	46	8	0	0	2	102	3,600	15	35	3	0	0	7	30	3,600	3,750	7					
12	Metzger and Vance, 1937	49 M		Palpitation	Weakness	+	+	0	0	2.91	1.70	3,750	38	51	7	1	0	0	0	4,000	4,000	1,000	7					
13	Metzger and Vance, 1937	60 M		Dyspnea	Weakness	?	?	0	0	1.18	?	1,250	36	44	4	0	4	12	0	50,000	5	8	0	0	4	83	0	1,400	117,000	20					
14	Miller and Seymour, 1937	37 F		Dyspnea	Weakness	+	+	0	0	2.34	2.33	7,450	12	37	0	0	0	41	0	3,250	61	23	5	0	0	8	6	2,400	5,750	8					
15	Miller and Seymour, 1937	21 M		Pain in leg	Weakness	+	+	0	0	1.30	1.53	5,100	65	25	2	0	2	6	18	3,750	30	10	1	0	0	40	13	2,550	75,000	12					
16	Miller and Seymour, 1937	23 M		Dyspnea	Weakness	+	+	0	0	1.07	2.90	7,700	63	28	9	0	0	0	0	4,700	2	39	2	0	0	0	57	6	2,600	11,300	12				
17	Miller and Seymour, 1937	60 M		Dyspnea	Weakness	+	+	0	0	2.39	3.40	2,600	24	52	0	1	0	23	10	8,900	52	15	0	0	0	4	27	2	1,300	8,900	9				
18	Miller and Seymour, 1937	69 M		Dyspnea	Weight loss	+	+	0	0	1.80	1.61	1,300	28	60	4	0	5	0	0	Greatly reduced	Greatly reduced				

leukopenia was a frequent finding. In 2 cases, however, manipulation of the leukocyte count by a toxic agent, *i. e.*, Staph. vaccine in the first case, and Staph. toxoid in the third case, gave increases in the number of leukocytes which tended to return to the normal level when the toxic agent was discontinued. In each case purpura was encountered at some time or several times during the course of the disease. Minor infections, such as gingivitis, sore throats, ulcerations of the buccal mucous membrane, furuncles and abscesses, were encountered in each case with the exception of the last one, and from 3 of these (Cases 1, 2, and 3) during the course of the illness *S. aureus hemolyticus* was cultured from these foci. During the terminal pneumonia in Case 4 this same organism was again cultured. We believe that this finding is evidence only of a secondary invasion with an organism which is truly widespread. However, its occurrence in these 4 cases, which were very similar, is at least worthy of note.

Transfusion was the mainstay of the treatment in each case. Only in 1 case was there a suggestion that something had been done to cause remission of the disease, but the remission which occurred in Case 1 lasted only 5 months. On the other hand, this remission, except for continued leukopenia, was complete.

Three bone marrow biopsies were done. One of the bone marrow biopsies was obtained from Case 2, in which no autopsy was done. The biopsied material from Cases 2 and 3 were similar: each showed hyperplasia and amaturation of the cellular elements. Each of these was done early enough in the disease to show less change in the red cell elements than that of the first case. The biopsied material from the first case showed more hyperplasia of the white cell elements and a surprising nonmaturation, as well as definite lack of red cell and platelet formation.

Where autopsies were obtained (Cases 1, 3, and 5), the greatest amount of disease was found in the bone marrow. Because of the minor infiltration in spleen, liver, and lymph nodes the disease appears to us to a large extent to be dysfunction of bone marrow.

A summary of the 13 cases in the literature and of these 5, is given in the chart. It will be seen that the duration of the disease of each of these is greater than the usual for myeloblastic leukemia. Absence of clinical enlargement of spleen, liver, and lymph nodes in each case is a striking factor, as well as is a tendency to leukopenia.

Summary and Conclusions. Five cases of leukopenic leukemia have been presented. The abnormal cells found in the blood of each of these were greatly embryonic or blast cells. By the appearance of such cells in Wright's stained specimens, in specimens stained with supravital dyes, and to a certain extent by the use of the peroxidase reaction, each case was designated myeloblastic leukemia. This diagnosis was confirmed in 4 cases by autopsy or bone marrow biopsy. The striking lack of involvement of organs other than the

bone marrow also seems to us to be proof of the myelogenous origin of the disease.

Auer bodies were found frequently in the blast cells of 2 cases (1 and 3), and were as readily recognized with the supravital dyes as with Wright's stain.

In each of the 5 cases the only effective therapeutic agent employed was transfusion and this was of value for only a short time.

We wish to thank the Institute of Pathology of Western Reserve University for the protocols of the 3 autopsies included in this report. We wish to give credit to Dr. W. B. Wartman for the micrograms.

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OBSERVATIONS ON BLOOD REGENERATION IN MAN.

III. THE RISE IN RETICULOCYTES IN PATIENTS WITH HEMATEMESIS OR MELENA FROM PEPTIC ULCER.*

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A RISE in reticulocytes generally is interpreted as a sign of an increased blood production. In the case of an acute hemorrhage, however, a certain rise must be expected even if blood production continues at a normal rate. Reticulocytes are supposed to be young, not quite ripened, perhaps prematurely emitted red blood cells. Their number generally is given as a percentage of the total red cell count, not as an absolute number. In normal conditions, we find up to 1% in man, or, with 5 million erythrocytes, 50,000 reticulocytes per c.mm. Now, if a patient after an acute hemorrhage has only 1 million red blood cells left, and if the production of reticulocytes continues at the same rate as usually, the same number of reticulocytes per c.mm. will give, not 1% but 5%. Furthermore, after an acute hemorrhage, the total blood volume probably is not made up at once but only the plasma volume. This, to be sure, will not give a higher reticulocyte percentage, but the red cell concentration will be higher than corresponding to the blood loss and with it the absolute number of reticulocytes per c.mm.

These facts must be borne in mind when reticulocyte counts are used to advocate an increase of production after hemorrhage.

* Supported by a grant from the P. Carl Petersen Foundation. Read at the meeting of the Danish Society of Internal Medicine, October 29, 1937.

Thus, 25% reticulocytes at a level of 1 million red blood cells means at most 5 times as many reticulocytes as normally, not 25 times.

This applies not only to reticulocytes but all young blood corpuscles must be present in a higher concentration after a hemorrhage than normally, even without any increase in production. This means that the average age of the blood cells as a total will be lower than in normal conditions. Only a certain proportion of old cells from before hemorrhage are left; the rest of the blood is made up by new cells. Not until regeneration is complete and normal level reached will the average age be as high as before the hemorrhage. Until then, it must be lower. If my earlier theories about regeneration^{13c} are correct, this period will correspond to the lifetime of the red blood cells.^{13c}

In the following are given a survey of the findings in literature, as well as my own reticulocyte counts in patients with hematemesis or melena from peptic ulcer.

Survey of Literature. In Table 1 are given the reticulocyte rises after experimental hemorrhage in animals.

TABLE 1.—RETICULOCYTE RISE AFTER EXPERIMENTAL HEMORRHAGE IN ANIMALS.

Species of animal.	Author.	Year.	Size of hemorrhage.	Retic. max. (%).
Rabbit . . .	Meulengracht ⁶	1918	1/18 of body wt.	20-30
Rabbit . . .	Torii ¹⁸	1923	1/67 of body wt.	8.6
Rabbit . . .	Gordon ²	1934	1/64 of body wt.	6.6-7.2
Rabbit . . .	Sjövall ¹⁵	1936	Repeated hem.	22-24
Dog . . .	Hoitink ⁵	1935	1/20 of body wt.	4.45
Sheep . . .	Wirth and Kangiera ²²	1936	1/24 of body wt.	3.4

The difference in maximal reticulocyte percentage between the different species of animals is considerable. A blood loss of about one-twentieth of the body weight induces only 3% to 5% reticulocytes in dog and sheep, against 20% to 30% in the rabbit. Wirth²¹ states that a horse after loss of one-half its blood has only 500 immature cells per c.mm., while the number in a dog which has been bled correspondingly is no less than 1 million.

In man, the figures found are varying (Table 2).

TABLE 2.—RETICULOCYTE RISE AFTER HEMORRHAGE IN MAN.*

Author.	Year.	Min. Hg. (%).	Retic. max. (%).	Comment.
Robertson and Bock ¹¹ . . .	1919	20	25.0	War-lesion
Heath ⁴	1933	35	25.0	Gastric hem.
Römcke ¹²	1933	26	9.0	Gastric hem.
Römcke ¹²	32	8.5	Gastric hem.
Römcke ¹²	36	8.5	Gastric hem.
Römcke ¹²	38	10.0	Gastric hem.
Römcke ¹²	70	10.0	Gastric hem.
Stadtmeister ¹⁶	1937	25	7.5	Gastric hem.

* The first two communications of Table 2 are those cited by most textbooks. My own figures, when no complications are present, correspond better to the last two.

Author's Observations. Technique. One-tenth centimeter of blood is mixed with 0.025 cc. 1% brilliant cresyl-blue. After 5 to 10 seconds a smear is made. Staining with Grünwald-Giemsa for 20 minutes. The countings have been made by three different technical assistants, but in almost all cases the same patient has been followed by the same assistant for the whole period of investigation. Hemoglobin and red cell examination as in former reports.^{13c,d}

Patients. The patients here investigated have been admitted to another department than were those of my earlier communications. As treatment they have been given a diet, consisting during the first days after hemorrhage of $\frac{3}{4}$ liter of milk and $\frac{3}{4}$ liter of oatmeal gruel. After 1 to 3 days, 1 liter of each was given and 2 eggs; later various milk soups and bread were added and the purée diet used by Meulengracht was attained 3 weeks after the feces had ceased to give a positive benzidine reaction. As to mortality (Olesen,⁹ Venndt¹⁹) and blood regeneration (when given iron^{13d}), these patients are comparable to those given the purée diet from the first day of admission (as in my first papers^{13b,c}).

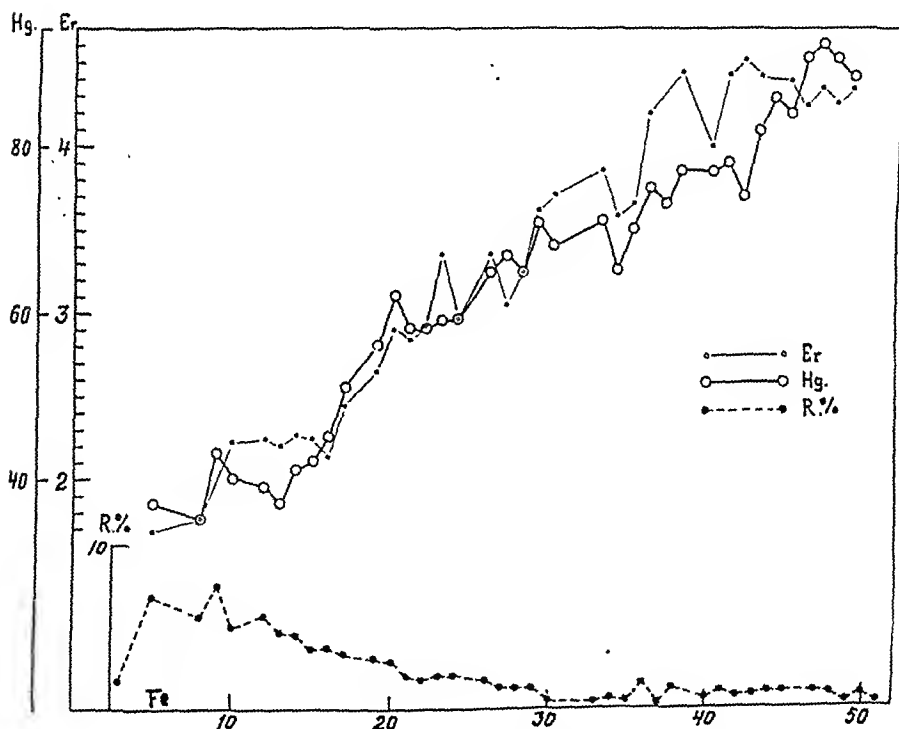


FIG. 1.—TYPICAL RETICULOCYTE CURVE AFTER HEMORRHAGE.

Reticulocyte percentage, number of red blood cells and hemoglobin percentage from patient with gastric hemorrhage from peptic ulcer. Abscissa: number of days after hemorrhage. Ordinate: reticulocyte percentage, red blood cells in millions per cubic millimeter, hemoglobin percentage.

Types of Reticulocyte Curves. In Figure 1 is shown a typical reticulocyte curve with hemoglobin and red cell values from a patient with gastric hemorrhage.

During the first days after hemorrhage, a certain reticulocytosis

is seen—perhaps due to the concentration of the reticulocytes mentioned in the introduction. By and by the percentage rises and reaches a maximum value, often plateau-like, about the sixth to eleventh day. After this, the percentage falls but for a very long time, up to 30 days, it keeps higher than normal. This is only what we might expect. Not until a lifetime of blood cells has elapsed will the average age of the blood cells be normal; until then, it will be lower because there is a greater percentage of younger cells and presumably also a higher reticulocyte per cent. The longevity

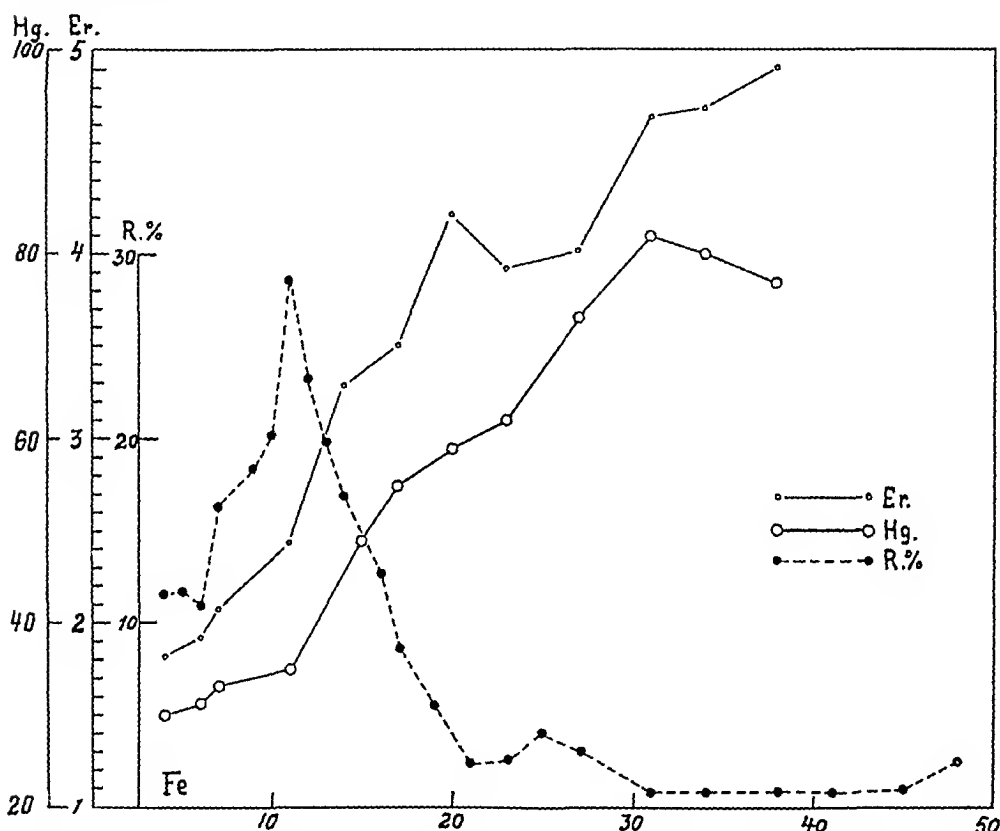


FIG. 2.—ATYPICAL RETICULOCYTE CURVE AFTER HEMORRHAGE FROM PATIENT WITH HYPOCHROMIC ANEMIA.

Abscissa and ordinate as in Fig. 1.

found in this way is about the same as that found by other methods.^{13c} Curves of this type have been met with in 17 patients who have been given iron and in 10 patients given no iron. In 6 patients given iron, I have seen reticulocyte curves of quite another type (Fig. 2).

Here we get, not only much higher maximum values than in the other patients, but also a veritable peak as seen in pernicious anemia or in simple achlorhydric anemia under specific treatment. Five of these 6 patients on admission (soon after the hemorrhage) had a color index which was low, from 0.87 to 0.77, averaging

0.82 ± 0.02 . In the patients of the first group, the average index on admission was 0.92 to 1.13, averaging 1.0 ± 0.02 . The patients with atypical reticulocyte curves thus in a very important respect differ from the main group. The sixth patient with this type of reticulocytosis had a normal index at the 2 first determinations on admission; later, his index was low; this generally is not seen in patients treated with iron.^{13a,b}

My idea is that these patients, before the acute hemorrhage, were suffering from an iron-deficiency anemia, and, as a sequence to this deficiency, a lowered blood cell production. When they are given iron, they react in the same way as patients with a simple achlorhydric anemia, with an increase in production and a reticulocytosis which in some of them has been very pronounced (Fig. 4). I am confident that they would have shown a rise in reticulocytes when given iron even if they had had no hemorrhage.

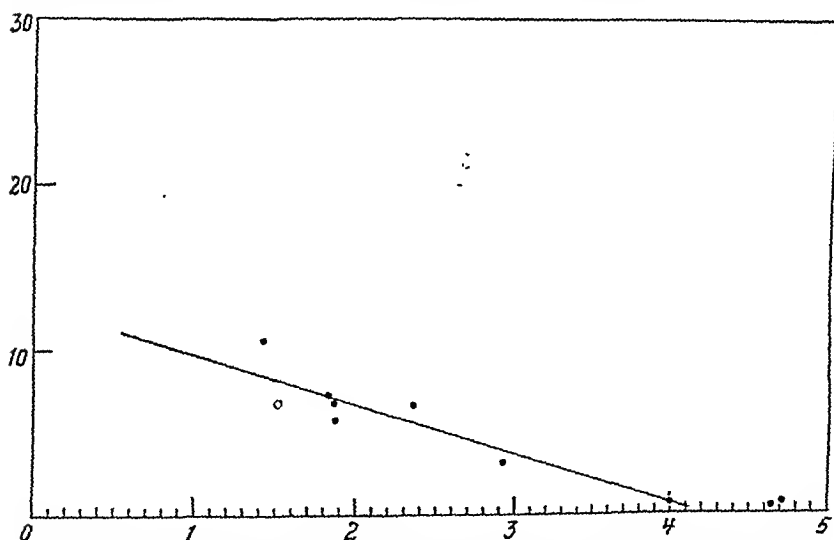


FIG. 3.—CORRELATION BETWEEN MAXIMAL RETICULOCYTE PERCENTAGE AND MINIMAL ERYTHROCYTE VALUE. PATIENTS NOT GIVEN IRON.

Abscissa: minimal erythrocyte value. Ordinate: maximal reticulocyte percentage. Solid circles: patients with a normal color index on admission. Hollow circle: patient with a low color index on admission. The line is drawn as an average.

One patient of the group not treated by iron, who had a low index (0.85), did not give a higher reticulocyte response to the hemorrhage than the other patients of this group (Fig. 3).

Correlation Between Maximal Reticulocyte Response and Minimal Erythrocyte Values. As in other anemias, the maximal reticulocyte percentage increases with falling erythrocyte values. In Figure 3, this correlation is shown for 10 patients not given iron. The reticulocyte percentage does not reach high values—only about 8% when the red blood cells are between 1 and 2 millions. This is

hardly twice the figure expected from the considerations given in the introduction. The line drawn as an average will be used as a standard in the following figures.

Those patients who have been given iron (Fig. 4) show a somewhat higher reticulocyte rise than the others, even if not as much higher as might have been expected. Many patients given iron do not rise higher than those not so treated (standard line). The 6 patients marked o had a low color index on admission or later. It will be seen that these 6 patients not only, as mentioned, gave another type of reticulocyte response, but also had definitely higher maximal values.

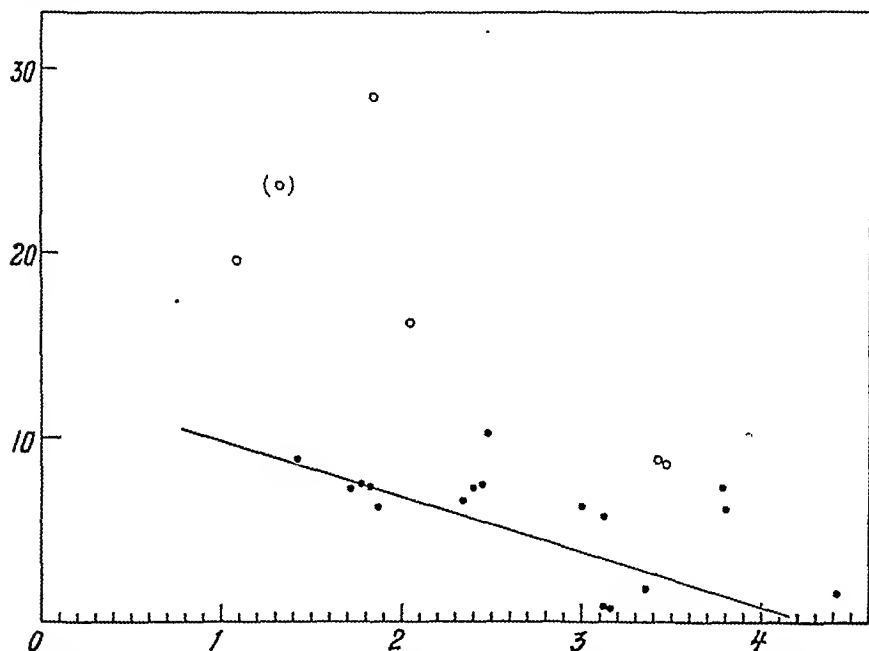


FIG. 4.—CORRELATION BETWEEN MAXIMAL RETICULOCYTE PERCENTAGE AND MINIMAL ERYTHROCYTE VALUE. PATIENTS GIVEN IRON.

Abscissa: minimal erythrocyte value. Ordinate: maximal reticulocyte percentage. Solid circles: patients with a normal color index on admission. Hollow circles: patients with a low index on admission or later (o). The line is the average from Fig. 3 (patients not given iron).

Some of the patients with a normal index also gave maximal values above the standard line. It is to be noted that many of these patients were admitted during the months of May and June. A moderate reticulocytosis during springtime has been seen in normals by Grunke and Diesing.³ These authors have found a rise from an average of 0.6% during the rest of the year to 0.9% in springtime; the maximal value found was 2.8%. Furthermore, Seyderhelm and Grebe¹⁴ have found that administration of vitamins (A, B and C) may promote a rise in reticulocytes. The higher values seen during May and June in our patients might have a similar explanation.

There is thus no great difference between the maxima attained in the iron group and the group without iron. In another respect, however, there is a difference between these two groups: The day of maximal reticulocyte value, reckoned from the day of hemorrhage, is somewhat later for those patients who have been given iron than for the others (10.6 ± 0.83 and 6.0 ± 0.73 days, respectively). Patients are given iron at once upon admission; but in many cases a few days elapse before the patients are admitted. If iron is given very late (*e. g.*, 10 to 14 days after the hemorrhage) a reticulocyte curve with two peaks may be seen. The first peak is seen about 6 days after the hemorrhage, the second appears 5 to 6 days after the iron medication has begun. This phenomenon has been described by Römcke.¹² Stadtmeister¹⁶ has seen a two-peaked rise in hematoblastic cells from sternal puncture under the same conditions.

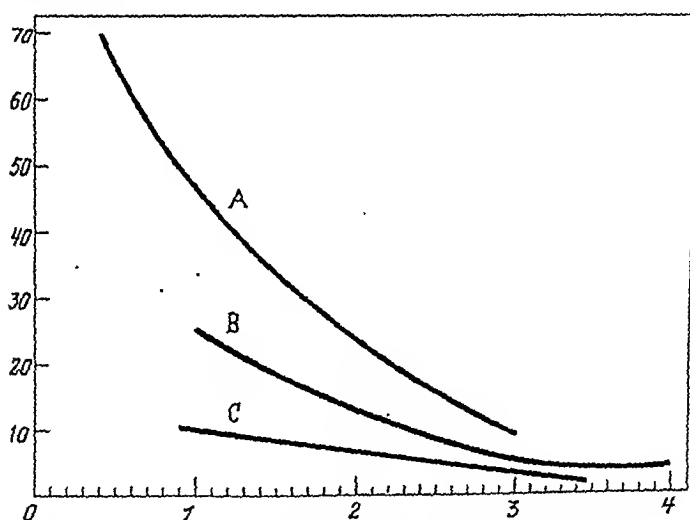


FIG. 5.—RETICULOCYTOSIS IN PERNICIOUS ANEMIA, SIMPLE ANEMIA AND ANEMIA AFTER HEMORRHAGE.

Abseissa: minimal red blood cell value. Ordinate: maximal reticulocyte percentage. Line A: pernicious anemia treated with liver intravenously (Minot and Castle³). Line B: simple anemia treated with iron (Heath⁴). Line C: standard line from Figs. 3 and 4 (anemia after acute hemorrhage, not given iron).

As will be seen from Figure 5, the rise in reticulocytes is but small after hemorrhage (even if treated with iron) as compared to the reticulocytoses seen in pernicious anemia or in simple achlorhydric anemia (Heath,⁴ Reznikoff and Goebel¹⁰). The correlation between lowest erythrocyte value and highest reticulocyte percentage is seen in all these conditions.

Reticulocyte Rise and Blood Regeneration Rate Compared. The regeneration rate of the individual patients may be expressed by the deviation from a known standard of the average daily rise in

red blood cells during the first 20 days after the minimal erythrocyte value was measured. This standard in the patients here investigated may be expressed by the equation:

$$\text{Daily rise} \times 33 = 4.8 - \text{minimal erythrocyte value in million} \\ (\text{Schjødts}^{13d})$$

Thus the maximal reticulocyte percentage may be compared to the regeneration rate. It may be said at once that in individual patients the connection between the two values is not evident. As an example may be given the figures from a group of patients who all started from about the same erythrocyte level and gave about the same reticulocyte response. The regeneration rate in these patients, on the other hand, varied greatly, the patients having been given different treatment.

TABLE 3.—RETICULOCYTE MAXIMA AND REGENERATION RATE IN 6 PATIENTS STARTING FROM THE SAME ERYTHROCYTE LEVEL AND GIVEN DIFFERENT TREATMENT.

Sex.	Age.	Minimum R.B.C. count (millions).	Retic. max. (%).	R.B.C. 20 days after minimum.	Reg. diff. fr. stand.	Iron.
F.	53	1.82	7.3	2.12	-62	-
F.	32	1.87	5.8	2.45	-51	-
M.	18	1.78	7.4	3.14	-19	+
F.	56	1.82	7.2	3.32	-4	+
M.	43	1.86	6.8	3.60	+6	+
F.	32	1.88	6.2	4.32	+41	+

The difference from the standard of regeneration is given in thousands of R.B.C.^{13c} The last patient differed from the rest in being from the country while all the other patients came from town. Besides, she was given ascorbic acid. I cannot as yet say if this has been of any importance.

Starting from the same point, the 20-day erythrocyte values varied from 2.12 to 4.32 millions. The first patient included in Table 3 hardly regenerated her blood at all, the last showed one of the fastest rises ever recorded. Still, they gave the same reticulocyte response. On the other hand, 2 patients with the same starting point and same regeneration rate gave maximal reticulocyte counts as different as 6% and 28% (the first patient was the last of Table 3, the latter one of those with a low color index).

Among the patients included in this investigation, those given iron regenerated their blood much better than those not so treated.^{13d} The reticulocyte response in the two groups, however, was not very different, even if somewhat greater in the iron-treated group.* Thus it is not possible in the individual instance to draw any conclusions from the reticulocyte rise as to the rate at which the patient will regenerate his blood.

It would be specially interesting if a better regeneration might be demonstrated during the springtime where we have seen a

* In 77 patients treated with iron since this paper was written, the reticulocyte rises have not been definitely higher than in the patients given no iron.

greater reticulocytosis. It looks as if this were the case, but nothing definitely may be said as yet.

Discussion. How is the reticulocytosis in these patients to be evaluated? Is it a sign of an increased production? The results included in Table 3 show that the same reticulocyte rise in one patient may be followed by a lively regeneration, in another by none at all.

The results of sternal punctures might indicate an increased production, as we here find the percentage of erythroblastic elements considerably increased after hemorrhage (Stadtmeister¹⁶). This author, however, finds a rise in erythroblasts even when no regeneration follows. Furthermore, the regeneration lines are straight and converging, which from theoretical considerations must be taken as a sign of a normal production rate.^{13c} An increase in production, to be sure, might be counterbalanced, *e. g.*, by a shorter lifetime of the old or new cells, or the surplus of production might be used to refill the depots which probably have been emptied after the hemorrhage.

I think reticulocytosis may be regarded as an earlier emission of the red blood corpuscles than normally; and I believe that such an earlier emission will often accompany an increased production. In the first place, the percentage of young (prematurely emitted) cells, which even at normal production rate is appreciable, will quite naturally be greater during increased production. Next, we may conceive that blood corpuscles during an increased production will be sent out earlier than otherwise, perhaps simply from overcrowding of the bone marrow. Finally, it might be imagined that the period of maturation during a crisis will be shortened when a bigger yield of cells is required.

Still, a reticulocytosis is not necessarily a sign of an increased production. I conceive of reticulocytosis at present as something by itself: a by-phenomenon to increased production when this is present, but a phenomenon which quite well may be seen alone. Thus, a reticulocytosis without any increase in the number of red blood cells is seen in pernicious anemia after administration of arsenic and so on (Minot and Castle⁷). By fractioning of liver preparations, we may get a factor which gives reticulocytosis but no regeneration; only after completion with other factors will regeneration start (Subbarow, Jacobson and Fiske,¹⁷ Eisler, Hammarsten and Theorell¹). Wichels and Höfer²⁰ found that reticulocytosis and regeneration responded differently after treatment, with different liver preparations. This dissociation between rise in reticulocytes and red cells has been mentioned by Murphy⁸ in 1933; but I do not think it has been demonstrated clinically as clearly as in the hemorrhagic anemias here investigated. Whatever the theoretical considerations may be, I think I have shown that the reticulocytosis in patients with acute hemorrhage is much less than previously assumed.^{4,11}

I can only conclude from all this that the output of the bone marrow must be the result of two factors: the intensity of production and the intensity of emission. These two are not necessarily always parallel and presumably they are controlled in different ways.

Summary. 1. After a hemorrhage, even if production of red cells is not increased, we may expect a rise in percentage of reticulocytes as the same (normal) number of reticulocytes will give a higher percentage when the erythrocyte level is lowered.

2. In the literature, the assumption of a high reticulocyte percentage (up to 25%) after hemorrhage has been a dominating concept.

3. In 17 patients given iron and in 10 patients not so treated, but all given the same standard diet, the reticulocytosis very rarely exceeded 10%.

4. As a contrast to these findings, 6 patients with a low color index on admission gave values up to 28%. These patients are supposed to have had an iron deficiency anemia before the hemorrhage.

5. The reticulocytosis in patients given iron did not greatly exceed that in patients not so treated.

6. A correlation was found between height of reticulocytosis and lowest erythrocyte level.

7. In individual cases, the size of the reticulocytosis did not give any indication as to regeneration rate.

8. The concept of reticulocytosis as an indicator of increased production has been discussed.

Technical assistance has been given by Mrs. E. Velleman, Mrs. A. Lachmann and Mr. J. P. Leth-Sørensen.

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PERITONEAL LAVAGE IN THE TREATMENT OF RENAL INSUFFICIENCY.

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PERITONEAL lavage as a therapeutic procedure in uremia was suggested by Ganter⁵ in 1923. The suggestion had for its basis the fact that urea, as well as certain other diffusible substances, may be removed from the blood by dialysis and the assumption that the peritoneum is a suitable dialyzing membrane.

The method has been tried very little except in the experimental laboratory. While there seems little hope that peritoneal lavage can replace renal function over a long period, it does appear possible that it may prove valuable in tiding a patient over a short period of renal insufficiency. In the type of acute nephritis sometimes seen in association with diabetic coma, in the renal failure occasionally seen after blood transfusion, in certain cases of bichloride of mercury poisoning, and in various other forms of urinary tract disease in which the ultimate prognosis is fair if the immediate crisis can be met, such a procedure might prove of real value.

We have carried out the procedure four times in 2 patients who were believed to fall in this group. Unfortunately, autopsy later proved the diagnosis in each case to be in error; but the chemical data obtained seems of sufficient interest to warrant this report.

Case Abstracts. CASE 1.—W. B. was a 68-year-old man admitted to Dr. Ravdin's service in this hospital in June, 1936. He was complaining of a 5-in. carbuncle of the back. Diabetes mellitus had been discovered 1 week previously. The past history was irrelevant. On admission, blood sugar was 300 mg. per 100 cc. and serum carbon dioxide 23 vol. %. A program was immediately instituted to control his diabetes and the carbuncle was excised. Within 12 hours it became apparent that he had a severe degree of renal failure with a blood urea nitrogen concentration of 100 mg. per 100 cc. Since there was no history suggesting chronic nephritis, as he had no cardiac enlargement, and did not have hypertension, it was believed that the renal failure was secondary to the diabetic acidosis, as in the cases reported by Holmes⁹ in 1935. Fluids were forced to 3 liters per day, sodium chloride and sodium bicarbonate were given in doses of 15 gm. each per day in an effort to promote kidney function, and sodium lactate was given intravenously to combat the acidosis. The urinary output was increased considerably, but the blood urea nitrogen concentration remained high in spite of these measures. Five days after admission the blood urea nitrogen reach 170 mg. per 100 cc., the patient became stuporous, and it was apparent that the customary methods of treatment had failed. Accordingly, on June 17, the patient was taken to the operating room and a cannula introduced into the peritoneal cavity under local anesthesia. Nine liters of fluid were introduced in 6 installments and a total of 6½ liters recovered.

The composition of this fluid is given in Table 1. Samples of blood were taken immediately before and immediately after the procedure and analyzed for serum carbon dioxide, serum chlorides, and blood urea nitrogen (Table 2). The lavage fluid withdrawn from the abdomen was analyzed for urea nitrogen, chlorides, and sugar (Table 3). Although the procedure required 2½ hours, it was well tolerated by the patient. The temperature was 102° F. before the procedure and 103° F. upon returning to the ward. The character of the patient's temperature curve was not altered by the procedure.

TABLE 1.—COMPOSITION OF LAVAGE FLUID EMPLOYED IN CASE 1.

Sodium chloride	14.5 gm. per liter
Potassium chloride	0.4 gm. per liter
Calcium chloride	0.2 gm. per liter
Lactic acid as sodium lactate	2.4 cc. per liter
Total chlorides	256.0 m.Eq. per liter

TABLE 2.—COMPOSITION OF BLOOD IN CASE 1 BEFORE AND AFTER PERITONEAL LAVAGE.

	Urea N, mg. %.	Chlorides, m.Eq./L.	Glucose, mg. %.	Carbon dioxide, vol. %.	Hemoglobin Sahli, %.
Before lavage	184	101	244	31	40
After lavage	155	116	272	29	42

TABLE 3.—COMPOSITION OF LAVAGE FLUID RECOVERED FROM THE PERITONEAL CAVITY IN CASE 1.

Urea N, mg. %.	Chlorides, m.Eq./L.	glucose, mg. %.
75	164	90

The pulse rate was 130 both before and after lavage and fluctuated very little in the interval. The respiratory rate was 44 before the lavage and 42 after it. The blood pressure was 130/70 before the procedure and was the same when the patient returned to the ward. The systolic pressure declined as low as 100 for a time during the lavage. The patient was completely stuporous at the start of the procedure, but toward the end he responded sufficiently to make a few intelligible complaints and upon returning to the ward responded to a question.

The subsequent course of the patient was downward and he expired the next day.

Autopsy revealed an advanced chronic glomerulonephritis. The peritoneal surfaces were smooth and glistening and no mark of the puncture could be found on the viscera. There was 300 cc. of fluid in the peritoneal cavity.

CASE 2.—W. H., a 34-year-old, white male, was admitted to the Abington Memorial Hospital for treatment of a right renal calculus. Ureteral catheterization failed to result in passage of the stone. Urinary output was scanty and blood urea nitrogen rose steadily. Hematuria was present but only a few casts were found. The clinical diagnosis was right renal calculus with oliguria due to reflex inhibition of the kidneys.

On September 22, 1937, pyelolithotomy and nephrostomy were performed. The urinary output continued to decline and the blood urea nitrogen continued to rise (Fig. 1). On September 24, moderate anasarca was noted which persisted. Gradually vomiting and mental confusion appeared. On October 7, the blood urea nitrogen rose to 223 mg. per 100 cc., the chlorides were 436 mg. %, and the serum carbon dioxide 33 vol. %. The total urinary output for 24 hours was 55 cc. Peritoneal lavage was performed, October 7, and repeated, October 8 and 10. Death ensued, October 12,

and autopsy showed an acute exacerbation of a chronic latent glomerulonephritis.

The patient seemed clearer mentally after the first lavage. Substantial quantities of urea nitrogen were removed, the chlorides and carbon dioxide values remained low. Portions of the lavage fluid used on October 10 (physiologic saline solution) were rendered hypertonic by the addition of glucose, the amount was not sufficient, however, to result in the withdrawal of body fluid. Four hundred cubic centimeters of one-sixth molar sodium lactate was also added in this lavage but without a significant effect on the serum carbon dioxide.

*Blood Urea Nitrogen
Concentration*

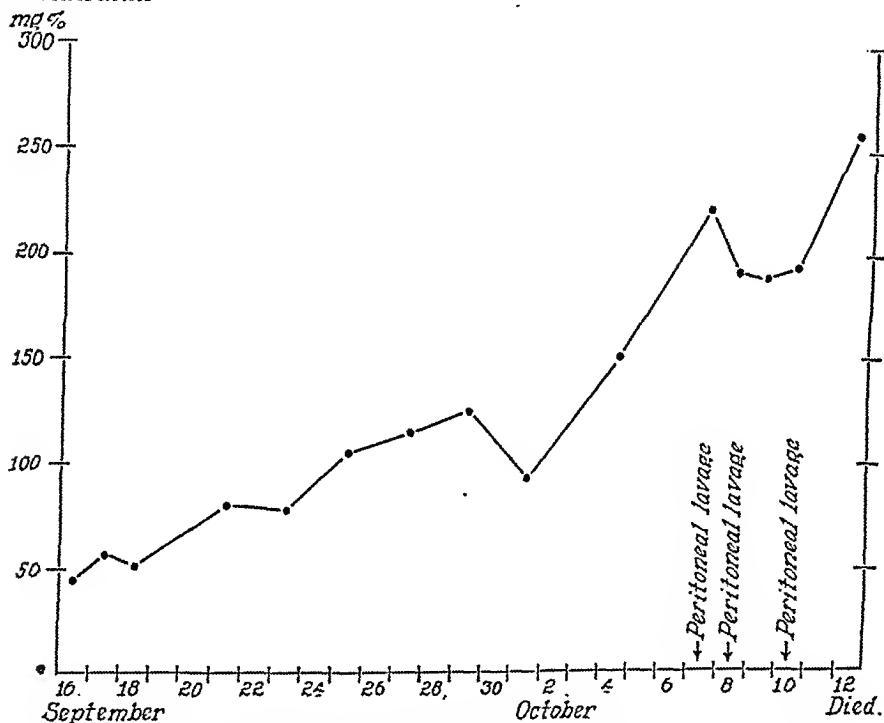


FIG. 1.—The course of the blood urea nitrogen concentration in the second patient. The terminal rise was checked for 72 hours by peritoneal lavage.

Blood specimens taken immediately before and immediately after each lavage showed declines in the urea nitrogen of 21.5 mg. %, 30 mg. % and 29 mg. %, respectively.

Peritoneal washings showed urea nitrogen values ranging from 174 to 195 mg. the day following lavage. analyzed 2 weeks later showed values of 7 to 10 mg. material decomposes at ice-box temperature.

Uric acid occurred in the lavage fluid in a concentration of 5 mg. %, which is of interest because Putnam¹³ stated that this substance did not dialyze through the peritoneum.

Discussion. Since the demonstration that glomerular function is largely a matter of filtration, artificial dialysis of blood naturally

suggests itself in line with other forms of substitution therapy. Dialysis of blood was first performed *in vivo* by Abel, Rowntree, and Turner in 1913-1914. A system of celloidin tubes was constructed and introduced into the circulation of dogs. Clotting was prevented with hirudin. These authors were especially interested in the method for the study of amino acids in the circulating blood.

Necheles¹¹ performed a number of animal experiments in removing nitrogen by shunting the circulating blood through tubes made of semipermeable membranes. Practical difficulties were encountered with anticoagulants. Haas⁷ used the method on 1 patient but felt that he could not be sufficiently sure of obtaining pure and harmless hirudin to employ the method widely.

Ganter,⁵ using rabbits and guinea pigs, and Landsberger and Gnoinski,¹⁰ using rabbits, produced a high blood urea nitrogen by various means (nephrectomy, ligation of ureters, uranium nitrate) and lavaged the peritoneum with the removal of substantial amounts of non-protein nitrogen and with temporary clinical improvement. Ganter applied the method to 1 uremic patient and to 1 patient with diabetic coma. He also replaced a collection of pleural fluid with saline in a uremic patient and obtained temporary improvement. Rosenak and Siwon¹⁴ extended these studies and recommended the use of 5% glucose solution at a temperature of 42° to 44° C.

More recently Haam *et al.*⁶ used peritoneal lavage as a method of treatment in acute uremia produced in rabbits with mercuric chloride. Fifty per cent of the treated rabbits recovered, as compared with 12% of the control group.

So far the method has been employed clinically in 13 cases (Table 4). The results substantiate the view that the procedure is futile in chronic nephritis, and other progressive forms of renal impairment. They do not prove or disprove the value of the procedure in those forms of renal disease in which the injury is temporary.

TABLE 4.—PERITONEAL LAVAGE IN THE HUMAN SUBJECT.

Author and year;	No. of cases,	Cause of uremia.	Result.
Ganter, ⁵ 1923	1	Chronic nephritis	Died
Heusser and Werder, ⁸ 1927	3	Not stated	Unsuccessful
Baláza and Rosenak, ³ 1934	2	Bichloride of mercury poisoning	Died
Wear <i>et al.</i> , ¹⁵ 1938	5	Carcinoma of bladder, 2	Died
		Bilateral hydronephrosis, 2	Died
		Reflex anuria with obstruction, 1	Lived
Author	2	Chronic nephritis	Died

The selection of cases is often difficult when the patients are first seen in uremia and suitable cases occur so infrequently that the experience of several clinics is needed to evaluate the method.

There is some justifiable hesitancy in performing abdominal

punctures, as fatalities have been reported.² However, most authors feel that the method is moderately safe in the absence of previous inflammatory disease of the abdomen and it has been employed many times to administer fluids to children and to some extent as a diagnostic procedure in abdominal diseases by Neuhof and Cohen.¹²

In both of the patients reported here the visceral peritoneal surfaces were carefully examined at autopsy for evidence of injury but none was found. In both cases the peritoneal surfaces were clean and glistening. The procedure had relatively little effect on temperature, pulse, respirations and blood pressure. It produced little discomfort, except during the second trial in the second patient, when the patient complained of some pain.

Both of these patients were shown at autopsy to have chronic glomerulonephritis and accordingly were unsuitable for treatment by peritoneal lavage. They, therefore, cannot properly be used for evaluation of the clinical results of this method. They do demonstrate, however, that the peritoneal cavity can be used in patients as a dialyzing membrane and that in the presence of high blood urea nitrogen concentrations substantial quantities of urea can be removed (Table 5).

TABLE 5.—UREA REMOVED BY PERITONEAL LAVAGE.

Lavage.	Fluid recovered, cc.	Concentration of urea, mg. %.	Total urea nitrogen, gm.
I	6,250	75	4.69
II	11,000	189	20.83
III	6,325	184	11.64

According to Bodansky,⁴ the 24-hour urea nitrogen excretion on a low-protein, high-carbohydrate diet can be reduced to the vicinity of 2.9 gm.

The real cause of death in uremia is still the subject of discussion. Surely the accumulations of urea in the body is not, as a rule, the decisive factor. Undoubtedly acidosis is an important factor, though whether this is the sole cause of death seems doubtful. A patient recently died of uremia at this hospital who had a normal serum carbon dioxide shortly before death. Since the normal kidney excretes only diffusible substances it is reasonable to assume that uremia is at least in part a disturbance of the concentrations of the diffusible components of the body fluids and if so should be amenable to correction by peritoneal lavage.

Urea was chosen for preliminary study because its concentration increases to such an extreme degree in renal insufficiency and because marked changes in its concentration are not brought about by many other conditions.

The basic solution used for peritoneal lavage should contain the diffusible components of blood serum in their normal concentrations and should theoretically contain a non-diffusible solute such as acacia in sufficient amounts to counteract the oncotic pressure of the serum proteins and so prevent the absorption noted in each of these four lavages. No practical experience has been had with acacia intraperitoneally but if it proves safe, hypertonic solutions might be effective in removing edema fluid from the body. Ideally, the lavage fluid should be especially prepared for each lavage on the basis of the chemical composition of the patient's blood serum. It should lack those solutes that need to be removed from the body, and contain those that need to be supplied, in relatively high concentrations.

It is interesting to note that although considerable urea nitrogen was removed the decline in the blood urea nitrogen was relatively small. Calculation shows that many times as much urea was removed as the decline in the blood urea nitrogen could account for, showing that large amounts of urea must be present in extravascular body fluids.

It is noteworthy that the lavage fluid attained a relatively high urea concentration although the average length of time between injection and withdrawal of installments of fluid was less than 15 minutes.

Conclusion. The history and rationale of peritoneal lavage are reviewed and the indications for its use discussed.

Two cases are reported in which it was employed. The method is recommended for further trial in cases of acute renal failure in which the prognosis for the recovery of the kidneys is fair provided the patient survives a limited period of renal insufficiency.

The author is indebted to Dr. I. S. Ravdin and Dr. Alexander Randall for permission to report the 2 cases and for many valuable suggestions. He is also indebted to the staffs of the Hospital of the University of Pennsylvania and of the Abington Memorial Hospital for their cooperation.

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THE CONCENTRATION OF THE INDIVIDUAL PHOSPHATIDES (LECITHIN, KEPHALIN, ETHER-INSOLUBLE PHOSPHATIDE) AND OF CEREBROSIDES IN PLASMA AND RED BLOOD CELLS IN PERNICIOUS ANEMIA BEFORE AND DURING LIVER TREATMENT.*

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DUE to the lack of suitable analytical methods, studies on the concentration of the individual phosphatides and of cerebroside of plasma and red blood cells in pernicious anemia have not previously been reported. The opportunity for such investigations was, however, established through the recent development by the author^{a,b} of approximate micromethods for determination of these lipids. The provision of such data in pernicious anemia appeared to be of considerable interest in view of the frequent occurrence in this disease of central nervous complications caused by scattered nerve-sheath degenerations in the white matter of the spinal cord. The inclusion in the study of analyses of the lipid constituents of the erythrocytes was further suggested by the recent demonstration of an abnormal permeability of the red blood cells in pernicious anemia, this abnormality disappearing during the liver treatment (Bang and Ørskov¹). The inclusion of cell analyses seemed also justified in view of the possibility that the phosphatides or cerebroside might constitute limiting factors in the erythrocyte formation, the deficient cell production in pernicious anemia supposedly being dependent on an insufficient synthesis of cell stroma.

The studies of previous investigators in this field have been limited to determination of the total phosphatide concentration of plasma (Bloor and MacPherson,² Feigl,³ Muller⁵). The observations by Bloor and MacPherson and by Feigl date from before the era of liver treatment, whereas the studies of Muller were on patients both before and during remission of the anemia caused by liver administration. The results of these authors are in agreement by showing a definite reduction of the plasma phosphatide values in several of the cases studied, this reduction occurring particularly in those cases presenting the severest degree of anemia (Muller). In the group of patients subjected to liver treatment by Muller, a rise of the phosphatide values to normal usually took place during the remission of the anemia, the increase generally occurring simultaneously with the reticulocyte rise and with an increase in the plasma cholesterol values, but occasionally somewhat later.

* An abstract of the paper was read before The 18th Medical Scandinavian Congress at Helsingfors, June, 1937. The investigation was aided by grants from the P. Carl Petersen Foundation and The Ella Sachs Plotz Foundation.

The present study includes observations on 14 patients with untreated or insufficiently treated pernicious anemia. Ten of the cases were followed for several months during administration of a potent liver extract. In 5 of the patients (Cases 138, 460, 336, 521, 528) definite signs of spinal involvement were present. Blood was usually obtained for analyses on 2 separate days before the onset of liver treatment and at various intervals during the remission. The liver preparation used was "Extractum hepatis 'Gea'," 1 cc. of extract, according to the statements of the manufacturers, being derived from 50 gm. of liver. One 10-cc. injection was given intramuscularly on each of 4 successive days, and this dose repeated when the rise in hemoglobin and erythrocytes had come to an end, which usually took place after a period of 3 to 4 weeks. The analyses were performed by a procedure developed by the author; for technical details reference is made to the brief outline given below and to the original publication.^{4a,b}

Method. The analyses, performed on heparinized plasma and erythrocytes, isolated by centrifugation, include determinations of total fat, total phosphatide, lecithin, kephalin, ether-insoluble phosphatide, and cerebroside. The blood samples were drawn in the morning during fast. The lipids were extracted from plasma and red blood cells with alcohol ether, and subsequently isolated in petroleum ether as described by Kirk, Page and Van Slyke. The total fat was determined gasometrically by combustion of the residue of an aliquot of the petrol-ether extract. Cerebrosides were estimated by a modification of Kimmelsiel's procedure, the reduction of the residue of an aliquot of the petrol-ether extract being determined by the method of Hagedorn and Jensen before and after hydrolysis with hydrochloric acid. For determination of the individual phosphatides, the following procedure was employed: The phosphatides were precipitated from the petrol-ether extract with acetone and magnesium chloride according to Bloor, and the precipitate treated with moist ether, which redissolved lecithin and kephalin. Lecithin was then estimated in the moist ether extract by saponification with barium hydroxide and subsequent choline analysis according to Roman, whereas kephalin was calculated as the remaining ether-soluble phosphatide, the total amount of which was determined by gasometric carbon analysis of the residue of an aliquot of the moist ether extract. The amount of ether-insoluble phosphatide was determined by phosphorus analysis of the fraction insoluble in ether.

The normal plasma and erythrocyte values obtained by this method have been reported elsewhere.^{4c} The average concentrations found in 20 normal individuals for lecithin, kephalin and ether-insoluble phosphatide were 19, 68 and 58 mg. %, respectively, in the plasma, and 32, 117 and 47 mg. % in the cells, these figures showing that the kephalin fraction both in plasma and erythrocytes constitutes the greatest phosphatide group. The cerebroside values of plasma in normal individuals were found to vary from traces to about 100 mg. %, whereas in the cells the variation was smaller with an average concentration of 51 mg. %

The hemoglobin determinations were performed with an Autenrieth-Hellige colorimeter, standardized by the gasometric method of Van Slyke and Hiller,⁶ 100% of hemoglobin corresponding to 18.5 vol. % carbon monoxide capacity. Reticulocyte counts were made before and every second day following the liver administration.

Experimental. The results of *plasma analyses* (Table 1) show definitely reduced *total phosphatide* values in 9 of the cases before treatment, this finding being in good agreement with the observations by Bloor and MacPherson, Feigl and Muller. In contrast to the finding by Muller, no certain relation was, however, observed between the degree of anemia and the phosphatide depletion. In all the cases presenting a reduced phosphatide content of plasma the values were found to increase to normal during the liver treatment. The *total fat* values in all the cases varied within the normal limits, this finding confirming the observations of Bloor and MacPherson and of Muller.

From the results of analyses of the individual lipid fractions it is seen from the table that no consistent changes were found to occur in the *lecithin*, *kephalin* and *cerebroside* concentrations of plasma. The figures, however, disclose the interesting fact that the value of *ether-insoluble phosphatide* occasionally was reduced in the untreated cases, and that in 9 of the 10 patients subjected to liver treatment a marked increase of this phosphatide fraction occurred during the treatment. The increase was noticeable 2 to 4 weeks after the onset of liver extract administration, thus occurring somewhat later than the reticulocyte response. The concentration of the ether-insoluble phosphatide finally reached values definitely higher than the average normal values (Fig. 1). In those cases followed for 5 to 6 months the figures were again found to approach the normal values. No difference in response was observed between the patients presenting spinal involvement and the uncomplicated group.

A similar, though less marked increase in the concentration of the *ether-insoluble phosphatide* fraction was occasionally observed in the *red blood cells*, whereas no consistent changes were found to occur in the *lecithin* and *kephalin* concentrations of the erythrocytes. The analyses of the red blood corpuscles, however, revealed the fact that *cerebrosides* were completely lacking in half of the untreated cases. In these patients, *cerebrosides* appeared in the cells during liver treatment. Furthermore, in all the cases but 1 the cerebroside values definitely increased during remission of the anemia. In interpretation of these findings it should, however, be recalled that the cerebroside concentration of the cells in normal individuals varies appreciably and that the procedure used for cerebroside determination, although less inaccurate than other methods available, probably is not quite specific.

Discussion. The investigations reported above have succeeded in demonstrating definite changes of the phosphatide concentration of plasma during liver treatment of pernicious anemia, and, similar though less constant, changes in the red blood cells. The change in plasma has been confined to the group of ether-insoluble phosphatide, a fact which appears of special interest in view of the presence of large amounts of sphingomyelin-like substances in the

nerve sheaths. A correlation between the improvement of pernicious anemia and the rise of this phosphatide fraction in plasma, therefore, appears to have been established.

In case of the red blood cells, the results do not permit conclusive statements in view of some uncertainty in the analytical method available for cerebroside determination. It would appear, however, that the cell constitution might frequently be definitely abnormal, a finding which is of interest in view of the demonstration by

*Mg. per cent Ether-insoluble
Phosphatide of Plasma*

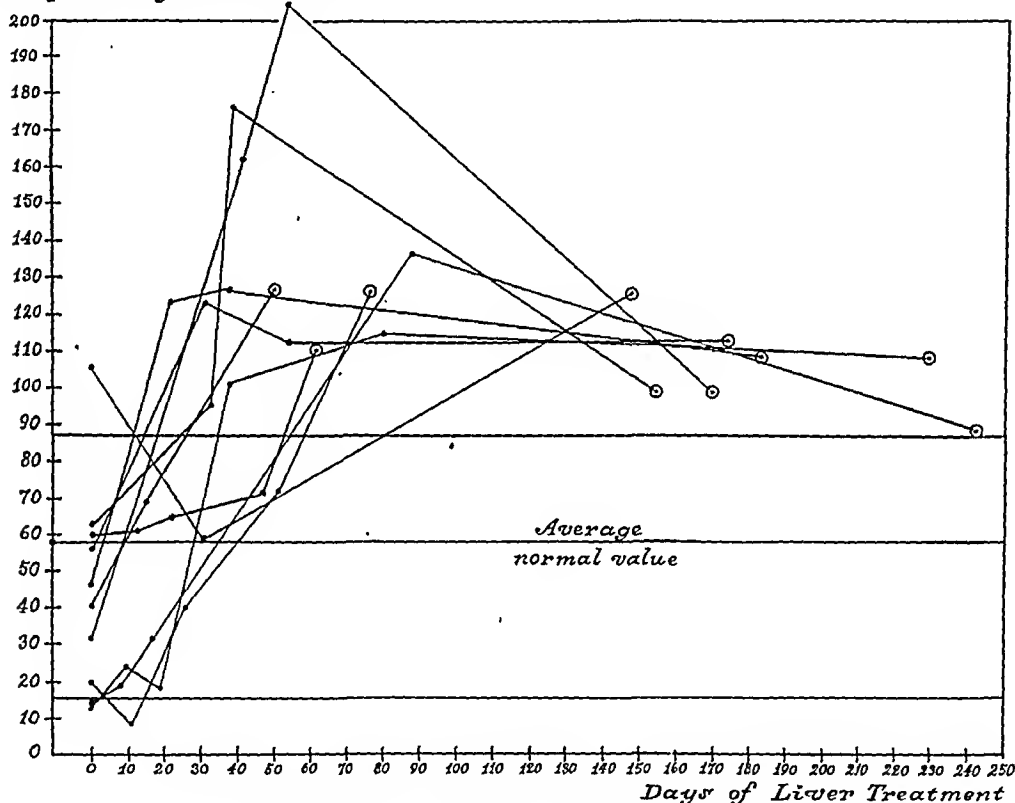


FIG. 1.—The concentration in pernicious anemia of ether-insoluble phosphatide of plasma during remission caused by liver treatment. The upper and lower horizontal lines limit the area containing 85% of the normal values.

Bang and Ørskov of an abnormal permeability of the erythrocytes in untreated cases of this disease. The interest is increased by the demonstration of a return towards normal of the lipid constitution of the cells during liver treatment, as a return of the erythrocyte permeability to normal was likewise observed by Bang and Ørskov concomitant with the remission of the anemia.

Summary. A study is reported of analyses of total fat, total phosphatide, lecithin, kephalin, ether-insoluble phosphatide, and cerebroside of plasma and erythrocytes in 14 cases of pernicious

TABLE 1.—THE CONCENTRATION OF THE INDIVIDUAL PHOSPHATIDES AND OF CEREBROSIDES OF PLASMA IN PERNICIOUS ANEMIA BEFORE AND DURING LIVER TREATMENT.

Hosp. No. (1937).	Initials.	Sex.	Age, yrs.	Atrophy of tongue.	Spinal cord involvement.	Liver treatment, days.	Hemoglobin, %.	Erythrocytes, millions per cmm.	Total fat, mg. per 100 cc.	Total phosphatide, mg. per 100 cc.	Leceithin, mg. per 100 cc.	Kephalin, mg. per 100 cc.	Ether-insoluble phosphatide, mg. per 100 cc.	Cerebrosides, mg. per 100 cc.
128. . .	T.O.L.	F	43	+	0	..	82 82	4.7 4.7	573 602	61 76	34	42 0	16 42	0
138. . .	E.C.	F	64	++	+	..	50 50	1.6 1.6	793 800	85 67	18 59	0 0	67 8	51
154. . .	T.S.	F	65	++	0	..	51 51	2.2 2.2	301 307	55 88	10 20	39 55	6 13	71 14
460. . .	M.P.	F	41	++	++	..	67 67	2.9 2.9	483 501	82 49	2 1	40 1	40 47	
355. . .	A.H.	F	60	+	0	..	37 37 11 26 51 77	1.2 1.2 2.1 3.0 4.1 5.2	518 686 476 554 520 688	68 146 147 187 139 138	39 99 83 45 21 3	0 36 56 102 47 9	29 11 8 40 71 126	4 0 0 0 0 39
393. . .	O.N.	M	64	0	0	..	38 38 10 19 38 80 230	1.2 1.2 2.0 2.7 3.4 4.9 ...	440 288 308 305 475 466 758	79 44 64 50 144 151 189	24 6 20 20 3 6 5	47 12 21 12 40 30 76	8 16 23 18 101 115 134	0 0 0 0 0 146
336. . .	T.C.	F	56	+	+	..	31 31 8 17 88 242	1.1 1.1 ... 1.9 4.4 ...	372 440 360 418 454 650	53 78 87 126 19 160	11 41 28 19 76 37	35 18 40 19 31 88	7 19 19 19 137 88	4 30 0 45
382. . .	I.H.	F	59	0	0	..	58 58 12 22 47 61	1.9 1.9 2.7 3.8 4.9 4.9	498 510 506 555 645 448	143 150 178 165 121 158	30 15 36 23 8 8	80 43 61 67 18 40	29 92 61 65 71 110	0 0 3 20 35
383. . .	F.B.	M	66	++	0	..	42 42 15 50	1.5 1.5 2.5 4.6	570 515 435 430	181 148 137 137	35 21 34 3	67 67 34 8	79 60 69 126	91 145 39 70
381. . .	C.H.	M	31	0	0	..	52 52 21 39 184	1.5 1.5 3.5 4.5 5.0	488 483 460 555 822	142 125 158 202 156	25 29 13 17 18	59 63 23 58 30	58 33 122 127 108	33 43 31 0 54
521. . .	S.F.	F	61	+	+	..	42 53 170	60 93 100 99	655 896 1020 752	84 275 334 154	35 73 54 11	17 40 74 44	162 162 206 99	13 234
448. . .	M.M.	M	51	0	0	..	58 58 31 54 174	2.1 2.1 4.0 4.8 ...	440 398 515 745 416	138 103 170 206 164	18 16 1 9	49 37 1 43	71 50 123 112	18 2 39 92
557. . .	L.N.	F	62	0	0	..	32 40 155	3.8 3.9 4.0 ...	461 406 596 702	77 117 263 152	4 3 33 11	11 19 60 42	62 117 172 99	65 98 28 29
528. . .	J.N.	M	57	+	+	..	56 85 30 148	1.9 1.9 4.0 4.9	542 353 431 615	147 127 125 156	1 1 14 15	27 52 59 125	119 94 57 46	125 62 57 46

TABLE 2.—THE CONCENTRATION OF THE INDIVIDUAL PHOSPHATIDES AND OF CEREBROSIDES OF RED BLOOD CELLS IN PERNICIOUS ANEMIA BEFORE AND DURING LIVER TREATMENT.

Hosp. No. (1937).	Initials.	Sex.	Age, yrs.	Atrophy of tongue.	Spinal cord involvement.	Liver treatment, days.	Hemoglobin, %.	Erythrocytes, millions per c.mm.	Total fat, mg. per 100 cc.	Total phosphatide, mg. per 100 cc.	Lecithin, mg. per 100 cc.	Kephalin, mg. per 100 cc.	Ether-insoluble phosphatide, mg. per 100 cc.	Cerebrosides, mg. per 100 cc.
128. . .	T.Cl.	F	43	+	0	..	82 82	4.7 4.7	372 378	62 85	0 41	46 26	16 18	34
138. . .	E.C.	F	64	++	+	..	50 50	1.6 1.6	494 241	56 151	23 89	11 39	22 151	0
154. . .	T.S.	F	65	++	0	..	51 51	2.2 2.2	198 345	64 198	6 4	38 175	20 15	7
460. . .	M.P.	F	41	++	++	..	67 67 72 56	2.9 2.9 2.6 4.5	478 558 404 398	157 121 249 236	64 121 76 8	76 61 161 178	17 56 12 50	0 68 34
355. . .	A.H.	F	60	+	0	..	37 37 55 26 51 77	1.2 1.2 2.1 3.0 4.1 5.2	503 201 345 505 412 348	130 69 167 296 160 186	20 18 32 95 1 25	56 20 124 169 13 96	54 31 11 32 146 65	0 51 44 94 89
393. . .	O.N.	M	64	0	0	..	38 38 50 19 38 80	1.2 1.2 2.0 2.7 3.4 4.9	148 310 297 422 338 326	64 109 166 194 167 146	27 8 16 17 58 7	16 68 115 67 146 35	21 33 35 110 88 104	0 0 23 52
336. . .	T.C.	F	56	+	+	..	31 31 36 50 88	1.1 1.1 ... 1.9 4.4	442 315 257 324 525	195 92 93 137 224	37 20 15 19 12	138 26 69 78 127	20 46 9 40 85	0 15 124
382. . .	I.H.	F	59	0	0	..	58 58 68 22 47 61	1.9 1.9 2.7 3.8 ... 4.9	420 233 434 308 352 352	165 83 296 183 126 177	5 2 58 4 9 6	132 19 146 71 3 54	28 62 92 118 112 117	0 0 23 20 40 72
383. . .	F.B.	M	66	++	0	..	42 42 61 50	1.5 1.5 2.5 4.6	488 505 292 202	142 286 121 52	3 20 0 8	80 163 10 8	59 103 111 36	26 72 48
381. . .	C.H.	M	31	0	0	..	52 52 92 39	1.5 1.5 3.5 4.5	279 359 286 409	86 139 107 205	0 20 4 39	48 81 6 93	38 38 97 73	63 42 33 158
521. . .	S.F.	F	61	+	+	..	60 93 53	2.1 4.8 4.8	304 298 452	122 113 309	3 10 20	70 68 163	49 35 126	37 104 53
448. . .	M.M.	M	51	0	0	..	58 58 87 54	2.1 2.1 4.0 4.8	278 324 368 350	55 125 215 201	2 3 2 17	15 26 98 111	38 96 115 73	0 3 88
557. . .	L.N.	F	62	0	0	..	38 78 84	1.4 3.9 4.0	428 605 427	242 210 216	13 9 8	54 156 96	175 156 112	13 94 103
528. . .	J.N.	M	57	+	+	..	56 56 85	1.9 1.9 4.0	378 468 432	195 278 247	9 25 40	107 173 180	79 80 27	21 17 51

anemia. In 10 of the cases observations were made both before and during liver treatment. In 9 of the 10 treated cases a marked rise in the plasma concentration of ether-insoluble phosphatide was observed 2 to 4 weeks following the onset of liver treatment. In one-half of the untreated cases cerebrosides were lacking in the red blood cells, but appeared during liver treatment.

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OBSERVATIONS MADE ON A GROUP OF EMPLOYEES WITH DUODENAL ULCER.

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THIS study is an analysis of the cases of duodenal ulcer diagnosed and observed at the Home Office of the Metropolitan Life Insurance Company from the year 1927 through the year 1936. All patients came from the personnel of the Home Office, which during the above period averaged 14,000. Of these, approximately 12,000 are engaged in executive or clerical work, and 2000 are employed in the Commissary, Building and Printing Departments. Ages of the personnel range from 18 to 70 years. The ratio of women to men is roughly $2\frac{1}{2}$ to 1 (Table 1). Although perhaps not representative of the whole population of this section of the country, this group offers variety as to age, occupation and race. On the average, they belong to the group of the economic population which consults general practitioners rather than clinics or specialists.

TABLE 1.—AGE DISTRIBUTION. METROPOLITAN LIFE INSURANCE COMPANY HOME OFFICE EMPLOYEES. AVERAGE PER YEAR.

Age.	Total.	Males.	Females.
All ages	13,885	3,965	9,920
17-19	1,185	65	1,120
20-29	8,420	1,775	6,645
30-39	2,045	910	1,135
40-49	1,310	680	630
50-59	740	390	350
60+	185	145	40

Employees with symptoms which suggested gastro-intestinal origin were referred for special study by other doctors in the Medical Division and by physicians of employees. In addition, many came

of their own initiative. From 1927 through 1936 a diagnosis of duodenal ulcer was made in 191 (7%) of the 2700 employees on whom gastro-intestinal fluoroscopic examinations were made. This percentage is considerably lower than that given by Eusterman and Balfour⁵ in their book, "The Stomach and Duodenum." On page 259 they make the following statement: "In a period of 12 months a review of 15,985 examinations of stomach revealed that 2047 or 12.2% had deformities of the duodenal cap characteristic of duodenal ulcer." It is possible, however, that the large number of employees referred to this department with chronic constipation as their only complaint might account for the lower percentage. It is surprising that almost half of the group were under the care of no doctor, or at best had made only one or two visits to their family physicians. As long as they could get relief from frequent meals and alkalies, they took care of themselves, though a second or third recurrence sometimes would bring them to the point of seeking professional advice. In each case, a history was taken and a physical examination was made before giving an appointment for the routine fluoroscopic, Roentgen ray or laboratory examinations. Only those in whom a typical (fixed) filling defect or niche of the duodenal cap or pylorus has been demonstrated have been classified as belonging to this group. Although many gave histories of earlier similar attacks, the diagnosis of ulcer had not been made previously in the majority. In the few instances where diagnoses had been made, the patients had not been led to expect a recurrence.

Once the diagnosis of duodenal ulcer was made, the nature of the disease, with emphasis on its tendency to periodicity, the symptoms of its more serious complications, and the importance of good general hygiene were explained. The necessity of putting themselves under the care of competent physicians was also stressed. If any complications arose while on duty which required radical treatment, these employees were referred at once to their doctors, clinics or hospitals. While all revisits to the Medical Division were voluntary, there has been opportunity for follow-up observation during the active course of the disease at the time of the check-up on dietary privileges, and during the remissions at the time of annual examinations. Fluoroscopic findings were checked periodically.

As has already been mentioned, only about half of this group have been under the care of any doctor, and only one-third of those who have received medical care more or less regularly have remained under the management of one doctor throughout the entire course of the disease. It has been evident that the physicians caring for this last mentioned group have made themselves familiar with the problems of the daily routines of their patients and have helped them to reconcile themselves to the ulcer regimen and in most instances take advantage of the facilities of the Company (extra feedings, fluoroscopic checks, sick leaves for rest, sanatorium care).

On the whole, treatment has been conservative. Surgery has not been advised until after medical treatment has been given an adequate trial and then only in cases of complications, such as repeated hemorrhages, perforation or obstruction.

As one would expect, a number of these individuals with ulcer have been difficult to treat, chiefly because of their impatience with the monotony of a régime. On the other hand, there have been some doctors who have not had the insight or taken the time to work out satisfactory and feasible plans for their patients. For instance, strict Sippy diets have been ordered for ambulatory cases and as a result, these employees, because of the impossibility of taking regular hourly feedings while at work, experienced pain and weakness due to insufficient nourishment. Other patients have been given vague ideas of the diets to be followed and believed that they were following instructions as long as they abstained from meat and drank plenty of milk. Some who have complained of pain have been afraid to eat, not realizing that frequent feedings were an important phase of the treatment. During the past 4 or 5 years some patients have received series of injections of histadine or emetine products with the assurance that their problem would be permanently solved. Naturally a recurrence of their ulcer pain has proved discouraging. While rest in bed on a Sippy diet* has been one of the most effective ways of ending an acute attack of ulcer pain and putting a patient on his feet, many general practitioners have failed to see the need for this type of treatment and their patients, discouraged, perplexed, and unfit to work, report to the Medical Division for advice.

Roughly speaking, we may say that in our population of about 14,000 there are 191 cases (1.38%) of chronic duodenal ulcer. Without a doubt this number does not include all of those with the disease. There are probably some whose symptoms are not severe enough to bring them to the Medical Division, some who either through fear or a sort of defiance refuse to admit to any illness, and some who are diagnosed and seen by their own doctors exclusively. But in view of the fact that the population under consideration numbers about two and a half times as many women as men, and that nearly 70% of the entire number is under the age of 30, we see further reason for regarding 1.38% as a low incidence for peptic ulcer, since a diagnosis is not made on a large percentage until after the third decade (Table 2). In the group of employees age 30 and over, we find a total of 2125 men and 2155 women, or practically an equal ratio (Table 1). The total of ulcer cases in this group numbers 81 men and 22 women, or 103 in all (Table 2). Here we find 103 cases of ulcer in a population of 4280 or an incidence of 2.4%.

* Emery³ reports 90% satisfactory results in patients who have been on complete Sippy; 85.1% on those on partial Sippy; and 80.1% in those on 5 meals and alkalies.

TABLE 2.—DUODENAL ULCERS. AGE AT ONSET OF SYMPTOMS AND AGE AT FIRST OBSERVATION. METROPOLITAN LIFE INSURANCE COMPANY
HOME OFFICE EMPLOYEES.

Age.	Onset of symptoms.		First observation.	
	Males.	Females.	Males.	Females.
Total	122	69	122	69
17-19	8	14	1	9
20-29	47	35	40	38
30-39	34	13	44	12
40-49	16	5	14	6
50-59	15	2	20	4
60-70	2	..	3	..

When we consider the fact that the ratio of males to females in the entire personnel is 1 to 2.5, and that of the 191 employees who have chronic duodenal ulcer, 122 (63.8%) are men, we find that the ratio of males to females in this particular group of ulcer patients is 4.5 to 1. This is higher than the ratios usually cited for peptic ulcer, although Eusterman and Balfour⁵ in their book write that "almost four times as many men as women harbor either duodenal or gastric ulcer."* Of the 14 gastric ulcers seen here in the past 10 years, all but 3 have been men. One male patient had both a gastric and duodenal ulcer.

One might expect to find the higher incidence of ulcer among the clerical and executive group, where many are supposedly under nervous or mental strain. However, the incidence of ulcer in the building group (4%) is higher than in any of the other three groups (Table 3), a fact which may be partially explained by the high percentage of men employed. This unit which is composed of engineers, carpenters, painters, electricians, elevator operators, and cleaning women cannot be said to represent the employees whose type of work subjects them to severe mental strain. The reports of Emery and Monroe⁴ and of Church and Hinton¹ show a large number of manual laborers.† A relatively high percentage of the building group (20%) suffered from hemorrhage and 8.8% underwent operation. This accounts for the high absence record, a total of 1658 days (39%) of the absences for the entire ulcer group.

Of the 191 cases, 9 men and 13 women resigned and so cannot be followed further. Three men and 2 women have retired, but can still be observed; there have been 5 deaths, none of which have been due to ulcer. During the first 8 months of 1937, 27 new cases have been diagnosed. This increase brings the total number under observation again to 191. Of these patients still under observation,

* Emery and Monroe,⁴ reporting on 1435 cases of peptic ulcer (1167 of duodenal ulcer, 215 of gastric ulcer, and 58 of both gastric and duodenal) give the ratio of male to female as 5.5 to 1.

† Emery and Monroe, in reporting on 1435 cases of peptic ulcer, list as occupations: manual labor, 703; clerical, 442; and housework, 290. Church and Hinton list chauffeurs, truckmen and automobile mechanics as highest (15%); clerks, cashiers, ticket agents, etc., 14%; and elevator men, janitors, porters, etc., as 8%.

82% have been followed from 5 to 10 years and have revealed a great variation in the periodicity of the disease in different individuals. In some, there has been a recurrence of symptoms almost every year, while in others remissions have lasted from 1 to 9 years.* However, once a typical constant filling defect of the cap is demonstrable by fluoroscope, it rarely disappears but remains much the same even during remissions. A change in contour of the stomach, the type of peristalsis, and a prolongation of emptying time are helpful in anticipating grave complications. Occasionally an irritable cap with a hazy outline and an irregular density is visualized in a patient whose history is typical of peptic ulcer. These patients are classified as cases of duodenitis, unless a typical deformity develops later in the course, as has sometimes been the case.

TABLE 3.—DUODENAL ULCERS. INCIDENCE ACCORDING TO OCCUPATION AND SEX. 1927-1936. METROPOLITAN LIFE INSURANCE COMPANY HOME OFFICE EMPLOYEES.

Occupation.	Total.		Males.		Females.	
	Cases.	Rate per 100.	Cases.	Rate per 100.	Cases.	Rate per 100.
Total	191	1.38	122	3.07	69	0.70
Clerical	138	1.15	78	2.94	60	0.64
Building maintenance	34	4.34	30	3.93	4	5.88
Commissary	9	1.53	6	2.73	3	0.82
Printing	10	2.30	8	2.40	2	2.00

TABLE 4.—DUODENAL ULCER. COMPLICATIONS AND TREATMENT. 1927-1936. METROPOLITAN LIFE INSURANCE COMPANY HOME OFFICE EMPLOYEES.

Item.	Total.		Males.		Females.	
	No.	%.	No.	%.	No.	%.
Total cases	191	100.0	122	100.0	69	100.0
Complications:						
None	163	85.3	104	85.2	59	85.5
Hemorrhage	20	10.5	14	11.5	6	8.7
Obstruction	5	2.6	3	2.5	2	2.9
Perforation	3	1.6	1	0.8	2	2.9
Treatment:						
Ambulatory	136	72.1	83	68.0	53	76.8
Bed	44	23.0	31	25.4	13	18.8
Surgery	11	5.8	8	6.6	3	4.4

Hemorrhage, the most frequent of the serious complications, occurred in 10.5% of these patients,† in 14 men and 6 women (Tables 4, 5, and 6). This diagnosis was not made unless there was a definite history of melena, with or without accompanying hematemesis, and subsequent low hemoglobin. In 11 instances, the bleeding occurred at the time of the onset of symptoms or within the following year; in 5 others, it occurred during the second or third year following onset. It was therefore most frequent early in the history of the disease. Hemorrhage occurred almost equally

* Emery and Monroe list 3 patients as going as long as 20 years without relapse.

† Eliason and Ebeling² report hematemesis or melena in 107 of 546 duodenal ulcers (19.5%).

at all ages. Recurring hemorrhages have occurred in 2 of the men and in 3 of the women. Only one of these last mentioned has undergone surgical interference, and ironically enough without relief; 1 patient has refused operation; 2, because of cardiac complications, were considered to be poor surgical risks; 1, a young man in his twenties who has hemorrhaged twice, was advised by his doctor to "wait." It has been over 2 years since he has had any symptoms.

TABLE 5.—DUODENAL ULCERS. TWENTY CASES COMPLICATED BY HEMORRHAGES. 1927-1936. METROPOLITAN LIFE INSURANCE COMPANY HOME OFFICE EMPLOYEES.

Sex.	Occupation.	Age at time of first hemorr.	No. of hemorrhages.	Year of ulcer history.*	Treatment.	No. of days absent.†
M	Cler.	20	1	1	Bed	49
M	Bldg.	21	2	1 and 3	Bed	110
M	Prtg.	22	1	1	Bed	160
M	Bldg.	25	1	1	Bed	181
F	Cler.	25	1	2	Bed	85
F	Cler.	27	4	9, 10 11 and 12	Transfusion Surgery	426
M	Cler.	30	1	3	Bed	29
F	Cler.	32	1	16	Bed	19
M	Bldg.	32	1	1	Bed	49
M	Cler.	33	1	5	Bed	34
M	Cler.	36	1	2	Bed	46
M	Bldg.	40	1	1	Bed	49
M	Comm.	43	1	2	Bed	50
F	Comm.	44	1	5	Bed	40
M	Comm.	46	1	1	Bed	59
M	Bldg.	54	2	1 and 2	Transfusion	197
F	Bldg.	54	3	1, 2, 3	Bed	145
M	Cler.	57	1	1	Bed	95
M	Bldg.	58	1	7	Surgery	159
F	Cler.	61	2	3 and 9	Transfusion	100

* Year of ulcer history represents the year during which the hemorrhage occurred.

† Total number of days lost in absent, 2082 (M., 1267; F., 815).

Eleven patients have been treated surgically, 8 men and 3 women (Table 6). Ages ranged from 21 to 58 years at the time of the first operation, with 5 (4 men and 1 women) in the sixth decade. All first operations, with the exception of 1 suture and 1 pyloroplasty with release of abdominal adhesions, have been posterior gastroenterostomies.

Three patients have had to have second operations. Case 8 (Table 6) had persistent epigastric pain following the suture of a perforating pyloric ulcer in 1930, but has been symptom free since a posterior gastroenterostomy in 1931. Case 9 had a recurrence of pain a year after his first operation, and returned to the hospital for a subtotal resection in 1934. Operative findings in 1933 were pyloric ulcer with obstruction; in 1934, a perforating jejunal ulcer. Up until now he has had no return of symptoms. Case 10, the third patient on whom a second operation was performed, was a young woman who was first operated on at the age of 21 for unrelieved pain. In 1933, 5 years afterwards, she had a severe hemor-

TABLE 6.—DUODENAL ULCERS. SURGICAL CASES, 1927-1936. METROPOLITAN LIFE INSURANCE COMPANY HOME OFFICE EMPLOYEES.

Case No.	Sex.	Occupation.	Age at onset.	Age at observation.	Age at operation.	Fluoroscopic findings.	Operation.	Surgical findings.	Year of operation.	Surgery recommended by:	Subsequent history.	Remarks
1	M	Cl.	41	43	43	Obstructive pyloric lesion	Post. gastro-ent.	Penetrating ulcer of pylorus	1934	H. O.	Negative	
2	F	Cl.	23	24	29	Defective cap.	Post. gastro-ent.	Duod. ulcer; obstr. at apex cap.	1934	Own M.D.	Negative	
3	M	B	28	32	32	Defective cap. constriction at apex	Post. gastro-ent.	Ulcer, ant. wall of cap.	1925	Own M.D.	Vague pain R. L. Q.; belching	Graham neg.; fluoro., high stoma
4	F	Cl.	20	56	56	Pyloric defect suggestive of malignancy	Post. gastro-ent., cholecystect.	Scar at pylorus; adhesions at site of old perf.	1927	H. O.	Constipation	Fluoro., no evidence of stoma, defective cap.
5	M	Cl.	58	58	59	Obstr. pyloric lesion; 24 hr. retention; dilated stomach	Post. gastro-ent.	Perforating pyloric ulcer	1934	H. O.	Negative	Operation advised a year previously
6	M	Cl.	54	58	65	Obstr. at pylorus; 24 hr. retention during attacks	Post. gastro-ent.	Duodenal ulcer	1935	Own M.D.	Negative	Fluoro., during remissions, defective cap., no obstruction
7	M	B	51	53	58	Pyloric ulcer	Post. gastro-ent.	Pyloric ulcer	1934	Own M.D.	Negative	Hemorrhage prior to operation
8	M	B	35	35	35	Diagnosis without fluor.	Suture	Perforating pyloric ulcer	1930	H. O.	Persistent pain	
				36	36	Post. gastro-ent.	1931	Own M.D.	Negative	
9	M	P	54	54	55 57	Pyloric lesion Jejunal ulcer	Post. gastro-ent. Subtotal resect.	Pyloric ulcer Perforating jejunal ulcer	1932 1934	H. O. H. O.	Return of pain Negative	
10	F	Cl.	18	21	22	Defective cap.	Post. gastro-ent.	Duodenal ulcer	1928	Own M.D.	Hemor. and transf., 1933, 1934, 1935	
				28	28	Stoma patent; stomach emptied well	Pylorect., partial gastrect.	Duodenal ulcer	1935	Own M.D.	Hemor. and transf., 1936	
11	M	Cl.	29	29	32	Duod. ulcer; obstr. 3d portion of duodenum	Pyloroplasty	Ulcer post. wall of duodenum; adhesions	1934	Own M.D.	Periodic attacks, responsive to medical régime	No response to medical régime prior to operat.

rhage which was treated by transfusion and rest in bed. In 1934, there was a repetition of this episode. When a third hemorrhage occurred a year later, a partial gastrectomy was done. Since this operation she has had to be transfused once for hemorrhage in 1936.

Case 11 did not respond well to medical regimen until after the removal of an acute appendix in 1931. From then until 1934 he had two minor attacks. In 1934 the pain returned. It was severe and was relieved only temporarily by complete bed rest. A pyloroplasty with release of abdominal adhesions has not prevented subsequent periodical attacks, but the pain now responds to the ordinary ulcer regimen.

A twelfth case, a man aged 55, should perhaps be classified with this group. Although he gave a vague previous history and operative findings in 1933 were reported as a "perforating pyloric ulcer, possibly malignant," autopsy at the time of his death in 1937 revealed a gastric carcinoma.

There have been no surgical deaths and the final results have been excellent so far in all but 3 cases, who have nevertheless been improved somewhat.

TABLE 7.—DUODENAL ULCERS. AVERAGE NUMBER OF DAYS LOST IN ABSENCE. TOTAL, UNCOMPLICATED AND COMPLICATED CASES. 1927-1936. METROPOLITAN LIFE INSURANCE COMPANY HOME OFFICE EMPLOYEES.

Age.	Total.			Uncomplicated.			Complicated.		
	No. of absences.	No. of days lost.	Average No. of days lost.	Ab-sences.	Days lost.	Average.	Ab-sences.	Days lost.	Average.
Total . . .	52	4165	80.1	25	878	35.1	27	3287	121.7
17-19 . . .	2	42	21.0	2	42	21.0			
20-29 . . .	20	1491	74.6	11	296	26.9	9	1195	132.8
30-39 . . .	10	376	37.6	5	144	28.8	5	232	46.4
40-49 . . .	7	397	56.7	3	55	18.3	4	342	85.5
50-59 . . .	12	1847	153.9	3	329	109.7	9	1518	168.7
60+ . . .	1	12	12.0	1	12	12.0			

DUODENAL ULCERS. AVERAGE NUMBER OF DAYS LOST IN ABSENCE. MALE AND FEMALE. 1927-1936. METROPOLITAN LIFE INSURANCE COMPANY HOME OFFICE EMPLOYEES.

Age.	Total.			Males.			Females.		
	No. of absences.	No. of days lost.	Average No. of days lost.	Ab-sences.	Days lost.	Average.	Ab-sences.	Days lost.	Average.
Total . . .	52	4165	80.1	38	2963	78.0	14	1202	85.9
17-19 . . .	2	42	21.0	2	42	21.0			
20-29 . . .	20	1491	74.6	12	692	57.7	8	799	100.0
30-39 . . .	10	376	37.6	8	347	43.4	2	29	15.0
40-49 . . .	7	397	56.7	6	357	59.5	1	40	40.0
50-59 . . .	12	1847	153.9	9	1513	168.1	3	334	111.0
60+ . . .	1	12	12.0	1	12	12.0			

Of the 191 cases, 139 have lost no time from work because of their ulcer symptoms. The 52 employees who have had absences because of this disease have lost a total of 4156 days during this 10-year period. This number represents less than 0.5% of the total number of days lost by all employees of the Home Office because of all illnesses during this period. Twenty-five employees without any complications lost a total of 878 days; and 27 with complications lost 3287 days or 79% of the total days lost. The length of individual absences has been in almost every case 10 days or more. Those in the age groups between 20 and 29 years, and between 50 and 59 years show the greatest number of days lost. The average number of days lost in the older group is slightly more than twice that of the younger group (Table 7). This may be explained by the greater frequency of the more serious types of complications occurring at this age. The number of days of absence among women in the 20-29 decade is considerably augmented by 426 days accredited to Case 10 of the surgical chart. Hemorrhage, occurring in 20 patients, accounts for a total of 2063 days, or 49% of the entire number of days lost.

Summary. 1. The analysis of this particular group of employees with chronic recurring duodenal ulcer is of value because of the opportunity for a complete follow-up in the majority of cases.

2. Correct diagnosis, together with conservative medical treatment, has kept most of the group comfortable. Unsatisfactory results were frequently due to inadequate management.

3. The incidence of chronic recurring duodenal ulcer, in the entire personnel is at least 1.38%, and is in all probability about 2%. Among the employees over age 30, the incidence of diagnosed cases is 2.4%.

4. The small percentage of cases which had complications was responsible for a substantial loss of time from work.

5. Severe complications have been relatively rare.

6. Hemorrhage, the most frequent complication, occurred almost equally in all decades from the third through the sixth, and was responsible for half of the total days lost from work.

7. The building group, representing skilled and unskilled laborers, showed the highest absence record, 39% of the total for the entire group.

8. Time lost from work because of chronic duodenal ulcer represents less than 0.5% of the total number of days lost by all employees for all causes during the same period.

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ANOREXIA NERVOSA AND PITUITARY CACHEXIA.

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Two cases will be described in which young girls with extreme cachexia, with many of the stigmata commonly ascribed to insufficiency of the anterior lobe of the pituitary, have regained normal health by increase in food intake without hormonal therapy. They are discussed in the light of clinical differentiation between pituitary cachexia (Simmonds' disease²⁵) and anorexia nervosa¹². In addition, certain disturbances not previously noted in such cases receive comment.

Case Abstract. CASE 1.—E. D. (Hosp. No. 92589), an American girl of Italian descent, aged 16, entered the New Haven Hospital on July 30, 1935, complaining of weakness and loss of weight which had started insidiously about a year earlier. The weight had fallen from 92 to 50 lbs. in a year. The patient believed that her height had not increased at all during this time. Anorexia had increased progressively to the point where appetite was practically non-existent. No cause for the anorexia was apparent. As the cachexia progressed she became constantly cold and sleepy, no longer had any interest in her usual daily routine, and became careless and slovenly in her habits. In the past 4 months there had been fairly marked loss of pubic and axillary hair. The menstrual periods, previously regular and entirely normal, ceased abruptly 3 months before admission to the hospital. For a month there had been marked shortness of breath on exertion and the patient consequently spent much of her time in bed. Several carious teeth had been removed during the year of the illness.

The patient had had rheumatic fever at 4 years of age but there were no other serious illnesses in the past. She had been seen in the out-patient department for routine examination at the age of 11 and again at 12 years. An apical systolic murmur was the only abnormality noted in these examinations. The height and weight were 48.5 inches and 50 lbs. respectively in 1930 and the corresponding values were 52 inches and 61 lbs. in 1931.

The family history contributed nothing of note. Her father, mother and 4 siblings were well. Most of them were rather short, though none were strikingly so. There was no history of endocrine abnormalities, congenital deformities, mental disturbances, gastro-intestinal disease, tuberculosis or diabetes.

Upon examination, the patient presented a strikingly cachectic, prematurely aged, appearance (Fig. 1). She weighed 48.5 lbs. and her height was 55.5 inches. The length of the extremities was proportional to that of the body. The temperature was 95.2° F. by rectum, pulse 50 and blood pressure 72/40. The skin was lusterless, dry, loose and inelastic. No abnormal pigmentation of the skin or mucous membranes was noted. The hair of the head was normal; the pubic hair was quite sparse and the axillary

hair almost entirely lacking. The eyes were sunken; the pupils, fundi and visual fields, normal. The palatal arch was high but not constricted, with teeth normal in number but with upper lateral incisors and canines reduced in size and abnormal in shape, said by the dental consultant to be typical of completely formed but dwarfed teeth. The thyroid gland could not be felt. The breasts seemed to have shared little in the otherwise generalized emaciation. The lungs were clear and the heart was normal except for a harsh systolic murmur heard over the apex only. The abdomen was normal. The external and internal genitalia were definitely underdeveloped. Edema was not present. Complete neurologic examination revealed no abnormalities. Psychiatric study yielded the impression of a normal mental status with nothing to suggest hysterical anorexia (questioning after recovery had started revealed that there had been listlessness, inactivity, inability to think clearly or to concentrate, and frequent spells of weeping for about 6 months, all of which was attributed by psychiatric consultants to endogenous depression superimposed on pituitary cachexia).

TABLE 1.—DATA IN CASE 1.

Date.	Height, in.	Weight, lbs.	Temp. °	Pulse.	Blood pressure.	BMR, %.	Blood.		Serum.						
							Sugar, mg.	NPN, mg.	Protein, %.	Albumin, %.	Fatty acids, m. Eq.	Lipoid phosphorus, mg.	Cholesterol, mg.	RBC, mills.	Hgb., %.
1935															
7/30 . . .	55.5		96.0	56	80/60	..	30	60	6.22	4.29	3.4	65
7/31	48.4	96.7	59	..	-34	26	3.6	70
8/1	47.3	96.7	83	95	64
8/2†	46.8	97.9	80	80/60	..	67	41	11.2	8.1	170
8/5	46.6	97.4	86	72/60
8/9	48.1	97.9	83	90/60	+3	3.2	70
8/13	50.6	98.5	90	90/60	-24
8/26	53.9	98.6	80	100/70	-12
8/30	54.3	98.3	80	100/76	-28	76	26	3.8	70
9/3†	56.3	98.5	73	98/70	6.68	4.58	11.4	9.7	..	3.3	68
9/11	57.4	98.4	82	78/48	-15	4.5	84
10/24	74.3	-3
12/5 . . .	55.8	87.5	86	31	7.58	5.04	16.3	11.4	249
1936															
8/6 . . .	57.4	85.0	102/80	-17	80	4.1	78
9/8 . . .	57.6	81.0	98/70	-7
1937															
10/23 . . .	57.6	103.3	94/64	-16	90	28	6.96	..	12.6	9.7	247

* Average of 3 or 4 observations daily while in the hospital.

† Excretion of PSP: 25% in 10 minutes, 85% in 2 hours. Urine spec. grav. 1.020.

‡ Hospitalization ended.

The Kahn test was negative. The blood contained 3.4 million red blood cells per c.mm., 65% hemoglobin (Sahli), and 4900 white blood cells per c.mm., with a normal differential count. Repeated urinalyses showed no abnormalities, the specific gravity of routine specimens reaching 1.020. Stools were negative. The basal metabolic rate was -34%. The fasting blood sugar on August 1st was 26 mg. % and when 25 gm. of glucose was given intravenously the following values were noted: at 30 minutes, 309 mg., at 45 minutes, 232 mg., at 90 minutes, 167 mg., and at 120 minutes, 146 mg. Serum calcium and phosphorus were normal. Blood non-protein nitrogen was 60 mg. %. Other chemical observations on the blood were all within the limits of normal (Table 1). A tuberculin test (Mantoux) was negative to 1 mg. The gastric contents after an alcohol test meal contained free HCl; fasting contents could not be obtained. Roentgen ray examination

of the skull was negative, the sella turcica being normal in size and shape; the bones of the arm and forearm were small but otherwise not remarkable; the lungs were clear and the heart rather small and quite vertical in position. Electrocardiogram showed low voltage of the ventricular complexes and a P-R interval of 0.29 second.

Treatment in the hospital was directed chiefly towards encouraging the patient to eat. Ferric ammonium citrate was given for the anemia and vitamin B supplements ("Bemax" and intramuscular liver extract) for their possible effects on appetite. On the 2d and 3d full days in the hospital the patient took 710 and 940 calories, respectively. On all other days, with two exceptions, the intake exceeded 1600 calories, varying between 2000 and 3000 after 2 weeks and exceeding 3000 calories per day during the last week in the hospital. The weight and strength improved rapidly and progressively after the first week of hospitalization; the pulse rate became normal on the 3d day; the temperature after 2 weeks; the blood pressure remained low, though the level after the 2d week was distinctly higher than it was earlier.

On discharge from the hospital, 6 weeks after admission, the weight had reached 60.5 lbs. and the chemical and metabolic abnormalities noted earlier had been corrected (Table 1). The electrocardiogram showed normal ventricular complexes and the P-R interval had fallen to 0.24 second. After 11 days in the hospital, when the diet was being fairly well taken, the fasting blood sugar was 65 mg.%, and 30 minutes after the intravenous administration of 25 gm. of glucose, it was only 186 mg.%, a normal value. Further samples were not taken.

She was studied subsequently in the out-patient clinic while undertaking increasing activity, treatment being limited to a high caloric diet and Bland's pills. Six months after admission to the hospital there had been a striking change in appearance (Fig. 2). She then weighed 90 lbs. and measured 56 inches and showed no abnormalities on physical examination. For laboratory findings then and subsequently see Table 1. Electrocardiogram showed normal complexes and a P-R interval of 0.20 second. When last seen, October 23, 1937, she reported that normal menstrual periods had started abruptly 2 months earlier. She has been working regularly and feeling fine. The diet has been unrestricted and the appetite has been so good that she has become a little more obese than she would like. A possible explanation for the onset of the anorexia was suggested during this interview. She says that she enjoyed grade school where she was among all her neighborhood friends but that high school became increasingly distasteful to her. During the summer and fall after her first year of high school she constantly begged her parents to allow her to leave school, but without success. This corresponds chronologically with the onset of the anorexia, although the patient was not aware of any causal relationship.

CASE 2.—V. S. (Hosp. No. A 66476), an unmarried American girl of Syrian extraction, aged 18, was referred to the hospital on July 21, 1936, on the advice of her physician, but against her own wishes. The history was obtained largely from her mother. The patient had apparently been quite well until about 2 years before admission. At that time she weighed 109 lbs. Because of difficulties with her family she voluntarily reduced her food intake with a resulting weight loss to 86 lbs., a year later, and to 58 lbs. on admission to the hospital. She disclaimed any appetite, going as long as 2 days at a time without any food, became moderately constipated and felt fairly weak. In spite of this she did not decrease her activities markedly and only 2 weeks before admission to the hospital played several sets of tennis. Nine months before this, menstruation ceased abruptly, having been slightly irregular but otherwise normal previously.

The past history contributed only the fact that the patient had always been a finicky eater. The family history revealed no abnormalities in stature or weight, no congenital deformities, endocrine disease, gastro-intestinal affections or diabetes. The aunt was said to have suffered from a "nervous breakdown" from which she recovered completely. The mother of the patient gave the impression of being a psychopathic personality of the hysterical type.



FIG. 1



FIG. 2

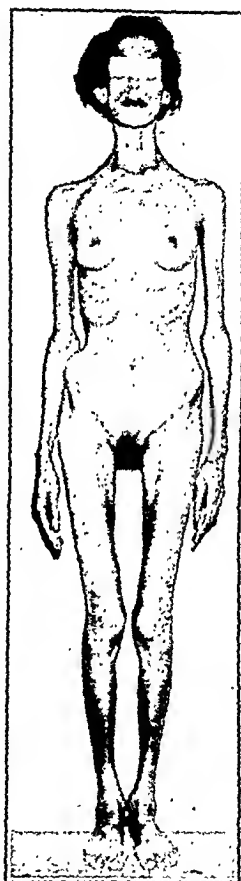


FIG. 3

FIG. 1. Case 1.—Appearance upon admission to hospital.

FIG. 2. Case 1.—Six months after admission to hospital.

FIG. 3. Case 2.—Appearance during first hospital admission.

On admission she was extremely emaciated (Fig. 3). The eyes were bright, staring and fairly prominent. The height was 60 inches and weight 57.9 lbs. Body proportions were normal. The temperature was 96.0° F. *per rectum*, pulse 50, and blood pressure 82/68. The skin was dry, lusterless and cold. The hair of the head was abundant, that of the axillæ and pubes scanty. The pupils, fundi and visual fields were normal. The teeth were in good condition. Only the isthmus of the thyroid was palpable. Examination of the lungs, heart and abdomen revealed no abnormalities. The

external genitalia were normal. There was no edema and the neurologic examination was negative.

Detailed psychiatric study of the patient revealed a psychopathic personality of the hysterical type with normal mental status. There was a strong mother-daughter attachment. The degree of psychopathology seemed much more severe in the patient than in the mother.

The Kahn test was negative. The blood contained 5 million erythrocytes, 91% hemoglobin (Sahli), 6200 leukocytes and a normal differential count. The urine was entirely negative, the specific gravity on admission being 1.015. Stools were negative. The basal metabolic rate was 23% below normal, the fasting blood sugar 70 mg.% and non-protein nitrogen 40 mg.%. Serum calcium, phosphorus and proteins were normal. Roentgenograms of the skull revealed a normal, small sella turcica, those of the spine and pelvis no significant changes and normal bony development for the age of the patient. The electrocardiogram was normal, with a *P-R* interval of 0.20 second.

Efforts to induce increased food intake were unsuccessful and the patient left the hospital against advice with her condition unchanged on August 15, 1936. Neither forced feeding nor forced separation from the mother was attempted. On November 30, 1936, she again came under the care of one of us (C.H.W.). At this time her condition was unchanged except that the weight had fallen to 54 lbs. and moderate anemia had appeared (R.B.C. 3.3 million, Hgb. 62%). She was admitted to the Lawrence and Memorial Hospital, New London, with the understanding that the mother was to be denied visiting privileges. The patient's hands were restrained and she was given water, salt and glucose subcutaneously and intravenously for 2 days, followed by liquid feedings by stomach tube for 11 days more. This liquid diet contained 80, 250 and 200 gm. respectively of protein, fat and carbohydrate daily and was supplemented by ABD vitamin capsules. Resistance to tube feeding diminished after a few days, and subsequently solid diet was fairly well taken voluntarily. An immediate weight gain of 7 lbs. in the first 3 days was undoubtedly due to the parental administration of salt and water, as is evidenced by a subsequent loss of 4 lbs. in the following week when parenteral fluid was omitted even though the caloric intake was very high. Furthermore, there was a sharp increase of 3 lbs. when 5 gm. of salt was added to the diet on December 13th to induce thirst. Concentrated liver extract (Lederle), 1 cc. daily, was given intramuscularly from December 10th to 15th without significant effect on the red blood count or hemoglobin, but with a reticulocyte rise to 4% on the 12th to 6% on the 16th (originally 1%). Since discharge from the hospital on December 23d, voluntary food intake has been excellent and the weight has risen steadily to reach 121.5 lbs. on March 22, 1938, when the B.M.R. was -19%. Menstruation had not been resumed at this time. The nervous difficulty has improved markedly and the patient has resumed her schooling. Theelin (2000 units a week) was given in August, 1937, in an unsuccessful attempt to restore menstruation.

A satisfactory sign to differentiate Simmonds' disease from anorexia nervosa has not as yet been established. The problem is the more difficult since cases of Simmonds' disease, established by autopsy, have rarely been subjected to extensive study in life. Almost all studies have been made years after the pituitary has been destroyed and when the effects of starvation are superimposed on those of pituitary deficiency. The physiologic disturbances to be expected from pituitary insufficiency *per se* cannot be predicted

unequivocally from the results of animal experimentation since even here results are often contradictory. The age at the time of hypophysectomy, the time elapsing since operation, and the effects of malnutrition have been neglected too often. An attempt will be made on the basis of analysis of proved cases of Simmonds' disease and of experimental work on the effects of hypophysectomy and of starvation to evaluate diagnostic criteria.

1. *Age Incidence and Etiologic Factors.* On the basis of autopsy experience, it seems hazardous, in the absence of demonstrable changes in the region of the pituitary or of syphilitic involvement of the brain, to diagnose pituitary cachexia except in women who have borne children. Simmonds' original case followed puerperal sepsis. The autopsied cases summarized by Silver²⁴ in 1933 show that, with the exception of the few instances in which the pituitary has been destroyed by tumors, the disease affects chiefly women in the child-bearing age, and frequently the onset can be related to a complicated pregnancy. Subsequent cases have corroborated this.

Anorexia nervosa, on the other hand, as originally noted by Gull, occurs most frequently in girls between the ages of 16 and 23 years. The detection of a psychologic background for the disturbance is often difficult. This is well illustrated by our own first case in which only after recovery was complete did the probable cause of the anorexia become evident. Sheldon²³ has intimated that many cases described as Simmonds' disease, particularly in early life, may well be instances of anorexia nervosa.

2. *Physical Activity.* Gull commented on the remarkable energy often noted in anorexia nervosa in spite of pitiful emaciation. Our second case showed a rather restless agitated state and a drive to continued physical exertions. The psychic status in anorexia nervosa is obviously as variable as the disturbances giving rise to the condition and the nature of the host. Since weakness and reduction of activity are the rule in pituitary insufficiency both in man and in animals, however, increased activity, when present, should help to exclude the diagnosis of pituitary cachexia.

3. *Response to Feeding.* Complete recovery through increased feeding alone was so striking in both our cases that the diagnosis of Simmonds' disease can be definitely excluded. That cachexia may be prevented by forced feeding after the destruction of the pituitary seems probable from the results of animal experiments^{5,16} and from the absence of serious loss of weight in proved cases of Simmonds' disease in which high caloric diets were given.^{4,11} Significant gain of weight as the result of forced feeding of cachectic hypophysectomized animals has not been described. Furthermore, that the cachexia of hypophyseal deficiency is not entirely secondary to diminished intake of food has been demonstrated conclusively in controlled paired-feeding experiments on rats.¹⁴ It seems justifiable to conclude, therefore, that if an important gain in weight occurs in a

cachectic patient as the result of increased food intake alone, pituitary function is not lacking.

4. *Response to Gland Extracts.* Cures in pituitary cachexia have been reported after administration of pituitary substance by mouth or of various extracts from the pituitary or the urine given parenterally. Such results actually indicate that the cases were not true Simmonds' disease. That pituitary substance *per os* is completely ineffectual in repairing any of the deficiencies produced by hypophysectomy in animals has been demonstrated by Smith.²⁶ Of the various disturbances related to deficiency of the anterior lobe of the pituitary gland, only the growth function can be completely restored in hypophysectomized animals over long periods by extract given parenterally. There is no clear evidence that even this function can be affected in man. Owing to the rapid development of anti-hormones, only transient effects on other functions are obtained with the extracts now available; permanent restoration of normal metabolic rate and resumption of normal ovulation, for example, can be produced in hypophysectomized animals by homoimplants only.

Wahlberg³⁰ has stated that functional insufficiency of the pituitary occurs clinically and that the administration of small doses of desiccated thyroid for a short period may restore normal function permanently. There is no objective evidence that such states exist and it seems probable that his patients had anorexia nervosa. Desiccated thyroid may raise the metabolic rate in true Simmonds' disease,^{19,20,31} but the clinical condition is thereby unaltered or aggravated.

5. *Physical Characteristics.* The cachexia and senile appearance of our patients, as in others with anorexia nervosa, differs in no essential manner from that described in Simmonds' disease. Nor is size a useful differential point. Pituitary insufficiency developing during the growth period should cause rapid cessation of skeletal growth, but the same must be true to a considerable degree in anorexia nervosa as it is in numerous conditions leading to malnutrition during the growth period (such as untreated diabetes, digestive disorders and repeated intercurrent infections). The scantiness of axillary and pubic hair often noted in anorexia nervosa is difficult to distinguish from the partial loss usually found even in well-advanced pituitary cachexia. Complete loss of pubic hair is a strong point in favor of pituitary origin for the cachexia, but lesser degrees of change must not be given undue weight in diagnosis. The preservation of the breasts in our patients, as in numerous reported cases of anorexia nervosa, contrasts sharply with the atrophy commonly noted in well-advanced pituitary cachexia, but atrophy is often found in starvation cachexia in age groups corresponding to those in which pituitary cachexia is commonly reported. It seems possible that disproportionate preservation of the breasts may exclude the diagnosis of pituitary cachexia.

6. *Disturbances of Function.* Our patients had diminution of basal metabolism, pulse rate, blood pressure and temperature quite as marked as those found in many proved cases of Simmonds' disease. None of these features serve to differentiate the two conditions. Hypophysectomy in animals produces a striking diminution of metabolism^{9,13} and subsequent thyroidectomy is said to cause a further small fall.¹³ The observations in proved cases of Simmonds' disease have been very variable, but in most instances have been between 30 and 40% below normal which is comparable to the levels observed in myxedema. Starvation, partial or complete, may produce depressions of this degree,¹⁵ and deficiency of protein alone⁸ or of vitamin B alone^{18,29} may cause considerable fall in metabolism independent of the caloric intake so that this is not a useful differential point. Fall in pulse and blood pressure parallel the reduction in basal metabolism rate in starvation. In a group of healthy young athletes on a diet only moderately deficient in calories, the average blood pressure fell to 94/60 in 3 weeks and the average pulse rate fell from 56 to 43 after 4 weeks, with one observation reaching 29.² These changes are quite as marked as those observed in pituitary cachexia. With resumption of unrestricted diet the blood pressure of these subjects did not return to normal until long after normal pulse rate and metabolism were regained. The hypothermia in our patients is as great as that noted in patients with Simmonds' disease. The specific dynamic effect of protein is not diminished by hypophysectomy¹ or by pituitary disease.¹⁰

Amenorrhea is present both in Simmonds' disease and in anorexia nervosa and is therefore of no use in differential diagnosis. In our first case menstruation ceased abruptly, and in the second after a period of oligomenorrhea. In both instances cachexia preceded the menstrual disturbance. Since wasting due to a variety of conditions frequently leads to amenorrhea, it seems unnecessary to assume any other causal relationship in wasting due to nervous anorexia. The reappearance of normal menstruation in the first patient is irrefutable evidence of pituitary activity.

7. *Carbohydrate Metabolism.* Our first patient had marked fasting hypoglycemia and an excessive hyperglycemic response to the intravenous administration of glucose. These abnormalities disappeared rapidly when the intake of food increased, confirming the impression that they were the result of starvation. Symptoms related to hypoglycemia were never noted in spite of the extreme depression of the blood sugar. Proved hypoglycemic reactions have not been observed in Simmonds' disease either, despite their frequent occurrence in hypophysectomized animals. The original diabetic tolerance curve of our patient might seem to exclude pituitary insufficiency, in which it is commonly accepted that the reverse type of curve is found. Recent experimental work indicates, however, that the apparent increased tolerance reported in this condition is actually

the result of delayed absorption from the gastro-intestinal tract.^{21,22} The glycemic response to intravenous injection of glucose in proved cases of Simmonds' disease has not been tested, but animal experiments indicate that hyperglycemia may be greater than normal.^{3,22} If this is true, the glucose tolerance test is a most uncertain aid in differentiation between Simmonds' disease and anorexia nervosa. On theoretical considerations the response to insulin should give a sharp differentiation, being increased in the former⁶ and decreased in the latter.²⁸ Actually clinical data are lacking to support this.

8. *Miscellaneous Comments.* Neither of our patients had demonstrable signs of vitamin deficiency, nor is such deficiency reported in anorexia nervosa. In complete starvation specific deficiencies have not been noted, probably because the reduced energy requirements are satisfied by body tissues which are complete foods. It is probable also, that the low level of metabolism in anorexia nervosa diminishes the requirement for vitamins. The requirements of vitamin B and C, at least, have been shown to vary definitely with the total metabolism.^{7,27}

It is apparent from the entire discussion that prolonged malnutrition in the intact subject simulates closely the changes attendant upon hypophysectomy. It seems possible that the occurrence of these changes during malnutrition represents a mechanism for conservation mediated through the pituitary, but there is no objective evidence to support this hypothesis.

Both of our patients had normal concentrations of proteins in the serum in contrast with the hypoproteinemia commonly associated with malnutrition. The normal concentrations do not imply that there was no deficiency of proteins, but only that they had been maintained in proportion to the blood volume. There was no apparent edema, although in the first case a decrease in weight from 48.4 to 46.8 lbs. in the first 48 hours suggests that there may have been subclinical edema. In the second case, the gains in weight in relation to salt intake seem somewhat excessive, and suggest the possibility that these patients might show malnutrition edema more commonly if they took normal amounts of salt and water. Serum lipoids in the first patient were at the lower limit of normal, rising moderately on recovery. Similar changes have been noted in simple under-nutrition.¹⁷

The blood non-protein nitrogen was moderately elevated in the first case and slightly above the usual limit of normal on ordinary diets (35 mg. %) in the second. The urine contained no albumin or formed elements in either case. In the first case, on the 4th day of hospitalization, when the N.P.N. was 64 mg. %, the excretion of phenolsulphonephthalein was 85% in 2 hours and a urine specimen shortly before the blood was sampled had a specific gravity of 1.020, which bespeaks a satisfactory ability of the kidneys to concentrate nitrogen. Unfortunately, chemical examination of the urine was

not performed. It seems possible to attribute the elevations of N.P.N. in the absence of demonstrable renal insufficiency to disturbance of circulation.

The electrocardiograms in the first case showed a striking prolongation of the *P-R* interval with return to normal during recovery from the cachexia. Since recovery, however, this has varied between 0.20 and 0.24 second which, in conjunction with the systolic murmur, small pulse pressure and rheumatic history, suggests that there may have been some myocarditis in the past. Prolongation of *A-V* conduction time is not typical of anorexia nervosa, as is evident from the fact that it is absent in our second case and in 2 other cases studied more recently in this clinic.

Summary and Conclusions.—Two cases of anorexia nervosa are reported in which the signs of Simmonds' disease were closely simulated. This was especially true of the first case in which there was no apparent psychologic background for the disease.

The diagnosis was established by the response to feeding.

It was suggested earlier by the obvious psychopathy and physical activity of the second patient, by the age of the patients, by the lack of etiologic factors for pituitary destruction and by the preservation of the breasts.

The depression of metabolic processes, disturbances of carbohydrate metabolism and suppression of menses have been shown to have no value in differentiating anorexia nervosa from Simmonds' disease.

Loss of pubic and axillary hair, if complete or almost so, suggests Simmonds' disease; sparsity or failure of development of this hair may occur in either condition.

It is apparent that no matter how strongly a patient's condition suggests Simmonds' disease skepticism is in order until adequate feeding has been given a fair trial; this is especially true in young girls, in whom anorexia nervosa is common and Simmonds' disease rare.

Cures with pituitary or thyroid extracts are evidence against, not for, Simmonds' disease.

Elevation of blood non-protein nitrogen, prolongation of *A-V* conduction time, and absence of hypoproteinemia and of obvious vitamin deficiencies receive comment.

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PHENOLPHTHALEIN STUDIES: PHENOLPHTHALEIN IN JAUNDICE.

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THERE are on record but few observations on the effect of phenolphthalein in jaundiced patients, and these are to be found in the early phenolphthalein literature. Tunncliffe⁶ reported 2 cases of obstructive jaundice in children in whom she claimed the usual phenolphthalein action was secured. Vivien⁹ described a similar observation. Elmer¹ observed 2 cases of catarrhal jaundice with acholic stools in both of whom phenolphthalein in the usual dose is reported to have produced a laxative effect. Suzor⁵ treated 1 patient with jaundice in whom phenolphthalein had a laxative effect, although the stools remained pale. Vamossy,⁸ Unterberg,⁷ and Mendelsohn,³ although reporting on different types of cases in which they used phenolphthalein as a cathartic, do not describe any cases with jaundice. From these meager observations the assumption has arisen that bile is not necessary for the action of phenolphthalein. Unfortunately, no estimate of the completeness of the obstruction is given in the reported cases; and it should be pointed out that the main causes of complete obstruction of the common bile duct, calculus and carcinoma, are rare in children (Tunncliffe's cases). Nor

is there any report as to degree of cathartic action secured from phenolphthalein when jaundice is present.

Because of this unsatisfactory state of our knowledge, and because of the practical importance of a decision whether phenolphthalein should or should not be used for therapeutic purposes in jaundiced individuals, and also because of the light such study might throw upon the way in which phenolphthalein becomes active, it seemed desirable to undertake carefully controlled studies to answer the question as to how important bile is for the cathartic action of phenolphthalein.

Method of Study of Clinical Cases. *Description of Patients.* This study was conducted upon 30 jaundiced patients of the medical wards of the Cook County Hospital who were given 0.3, 0.6, and 1.2 gm. doses of phenolphthalein. Each patient underwent the usual hospital procedures as to history, physical and routine laboratory examinations. In addition, various special tests indicated in jaundice cases were performed (icterus index, blood cholesterol determination, dextrose and galactose tolerance tests, and albumin-globulin ratio determinations). Some of these special tests were done repeatedly. An icteric patient who had acholic stools and no urobilin in the urine on repeated examination was classified as one with obstructive jaundice. The diagnoses were checked at certain intervals by the clinical course, operative finding, and necropsy (in some cases). After a preliminary observation of several days during which the routine clinical studies were undertaken, and the bowel habits were noted and a preliminary 24-hour urine specimen was obtained, the patients were given phenolphthalein.

Phenolphthalein Dosage. Each patient obtained a bedtime dose of phenolphthalein, his 24-hour urine specimen was collected, and the number of bowel movements during the 24 hours were recorded. In the majority of cases at least one of the stool specimens was examined daily for its bile content. After several days, when no more phenolphthalein was excreted in the urine, a second dose of phenolphthalein was given and the same procedure followed. The second dose was usually equal to twice the first. The preliminary dose, which at first was 0.3 gm., was later increased to 0.6 gm. Later the majority of patients received a first dose of 0.6 gm. and a second dose of 1.2 gm. In cases of doubtful results, as to number of bowel movements, the dose was repeated. No patient received more than 1.2 gm. at one time. During the period of this study, the patients remained on the same diet and medication, but received no other cathartics.

Procuring of Specimens. Regardless of whether the patient was ambulatory or confined to bed, he received a gallon bottle with a preservative (xylol) in it at his bedside; and was instructed to empty all urine voided into this container. The patients were also required to note the number of bowel movements in 24 hours. Every 24 hours these containers were emptied by one of us (F. S.), the amount of urine was measured, and a sufficient quantity together with the supernatant preservative taken to the laboratory for the various tests enumerated below.

Examination of Specimens. In addition to the routine urine examinations in the laboratories of the medical wards, the examination of the urine samples consisted in the determination of color, specific gravity, pH and NaOH values, conjugated phenolphthalein, free phenolphthalein, and albumin. The color of the urine was a useful index of the course of the patient's jaundice. The urinary albumin determinations showed that in patients, with livers damaged by disease, no albuminuria developed after the taking

of large doses (1.2 gm.) of phenolphthalein. This confirms the observations by Fantus and Dyniewicz²: that this drug does not produce kidney damage; as well as the conclusion of others that phenolphthalein may be a cathartic of choice in albuminuric patients.

Results as to Cathartic Action. It appears necessary to divide our series of cases into three groups:

Group 1: Cases of proved obstructive icterus (Table 1); the diagnosis confirmed by operation or necropsy, or both.

TABLE 1.—GROUP 1. CASES OF PROVED OBSTRUCTIVE JAUNDICE.

Case.	Diagnosis.	Dose in gm.	Total phenolphthalein eliminated in urine.		Resulting stools.
			mg.	% of dose.	
M. K.	Ca. of hepatic duct	0.30	59.80	4.43	Soft
		0.45	Soft
		0.60	Soft
M. D.	Ca. of head of pancreas	0.30	72.20	5.34	None
		0.45	None
		0.60	None
		0.60	None
C. F.	Ca. of gall bladder with duct compression	0.30	26.43	1.94	Soft
		0.45	Soft
		0.60	Soft
J. H.	Ca. of common duct	0.60	19.20	3.20	Soft
R. C.	Ca. of extrahepatic bile ducts	0.60	9.29	1.55	Soft
C. K.	Ca. of head of pancreas	0.60	5.1 (inc.)	0.85	None
C. H.	Stone in common duct	0.60	16.26	2.71	Soft
		1.20	97.53	8.12	Soft
F. K.	Ca. of head of pancreas	0.60	92.91	15.48	None
		1.20	134.51	11.21	None
G. M.	Ca. of head of pancreas	0.60	19.25	3.21	?
		1.20	11.65	0.97	?
R. G.	Ca. of head of pancreas	0.60	74.20	12.36	None
		1.20	None
L. P.	Ca. of colon, compression of common duct by metastases	0.60	30.65	5.11	None
		1.20	78.80	6.57	Soft
		1.20	Soft
H. R.	2 stones in common duct. Slight jaundice	0.60	29.85	4.97	Soft
		1.20	27.97	2.33	Liquid
W. S.	Common duct stone	0.60	50.47	8.41	None
		1.20	None
S. A.	Ca. of gall bladder with obstruction of ducts	0.60	None
		1.20	None

In patients with obstructive jaundice phenolphthalein does not, as a rule, produce marked cathartic action.

Group 2: Cases of probable obstructive icterus (Table 2): patients who clinically suggested an obstructive jaundice, but in whom the possibility of hepatosis (liver parenchyma damage) also had to be considered. Of these patients none were operated upon, and on the 2 who died no necropsy was permitted.

Group 3: Cases of hepatosis jaundice, *i. e.*, patients with definite disease of the liver parenchyma.

As will be seen from the subjoined tables (1 to 3), there were 14 cases with proved obstructive jaundice, 11 cases with probable obstructive jaundice, and 5 cases of hepatosis jaundice. Because

the bowel habits in these groups of jaundiced patients were very variable—with constipation, however, predominant—the results of this study were carefully checked; and, as mentioned above, in case of doubt rechecked with another similar dose of the drug. It was found that in some patients, who during the preliminary observation had 1 to 3 very small, hard stools daily or every other day and who on account of this felt constipated, the dose of phenolphthalein would lead to a softening of the stool but not to an increase in the number of movements. In other patients with similar bowel habits, even a softening of the stools failed to occur, while still other patients would remain without a bowel movement for 1 to 3 days, in spite of having received a large dose of phenolphthalein during this time. In a small number of patients, there was a laxative effect.

TABLE 2.—GROUP 2. CASES OF PROBABLE OBSTRUCTIVE JAUNDICE.

Case.	Diagnosis.	Dose in gm.	Total phenolphthalein eliminated in urine.		Result- ing stools.
			mg.	% of dose.	
L. B.	Obstructive, toxic jaundice	0.30	183.90	13.63	None
		0.45	None
		0.60	None
		0.45	89.95	19.10	None
J. B.	Ca. of head of pancreas	0.30	None
J. M.	Common duct stone	0.30	51.60	5.73	Soft
		0.60	Soft
S. K.	Malignancy or stone of com- mon duct	0.30	71.23	7.92	Soft
		0.60	Soft
F. K.	Common duct stone	0.60	67.45	11.24	Soft
F. W.	Gall bladder malignancy	0.60	51.65	8.61	?
		1.20	69.52	5.80	?
E. S.	Gall bladder stone or malig- nancy	0.60	26.28	4.38	Soft
		1.20	93.21	7.77	Soft
J. F.	Common duct stone	0.60	18.45	3.07	Liquid
A. M.	Ca. of gall bladder or toxic hep- atitis	0.60	7.70	1.29	?
		1.20	?
C. M.	Cholangitis or common duct stone	0.60	21.32	3.56	Soft
		1.20	19.38	1.62 (inc.)	Soft
L. S.	Cholangitis or common duct stone	1.20	66.92	5.58	Soft
		0.60	55.28	9.21	Soft
		1.20	114.95	9.58	Soft

In cases with probable obstructive jaundice phenolphthalein usually does not have a marked cathartic effect.

Summarizing the result, it may be stated that:

1. Of 14 definitely obstructive icterus cases (Table 1), 6 had no evacuation after a liberal dose of phenolphthalein; 7 had mere softening of the stools; and 1 had a questionable result because bowel movements were also reported as being rendered soft and frequent as a result merely of the ingestion of fruit.

2. Of the 11 probable obstruction cases (Table 2), 2 had no results whatever, 5 had mere softening of the stools, 2 had appar-

ently an increase in the number of stools, and in 2 cases the result is questionable.

3. Of the 5 hepatosis cases (Table 3), only 1 case showed no results, while the other 4 had both softening of stools and increase in the number of bowel movements, or liquid bowel evacuations.

TABLE 3.—GROUP 3. CASES OF HEPATOSIS JAUNDICE.

Case.	Diagnosis.	Dose in gm.	Total phenolphthalein eliminated in urine.		Result- ing stools.
			mg.	% of dose.	
A. S.	Cirrhosis of liver	0.30	Liquid
		0.60	62.86	6.98	Liquid
		1.20	64.21	5.35	Liquid
C. M.	Arsenical hepatitis (Carbarsone?)	0.30	None
		0.60	61.85	10.30	None
E. D.	Hepatitis (explored: no ob- struction seen)	0.60	12.05	2.01	?
		1.20	14.34	1.19	Liquid
N. U.	Toxic hepatitis	0.60	14.70	2.45	?
		1.20	?
		?
M. L.	Cirrhosis. Malignancy of liver. Luetic hepatitis	0.60	19.15	3.19	Liquid
		1.20	31.97	2.66	Liquid
		1.20	Liquid

In patients with jaundice due to liver degeneration, phenolphthalein usually produces a marked cathartic effect.

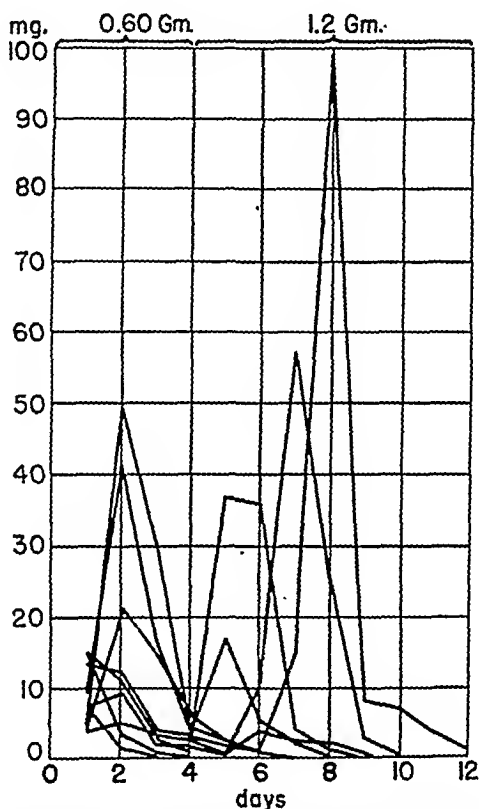
During remission of the obstruction in patients of Groups 1 and 2, cathartic effect from phenolphthalein was obtained as soon as bile appeared in the stools in the very individuals who had no evacuant action while the stools were completely acholic. Thus, 1 patient with common duct stone had good laxative effect with 1.2 gm. of phenolphthalein during a remission of her symptoms. Two patients of the second group who were quite cleared up from the jaundice had definite laxative effect with softening and increase in the number of stools from a dose given at that time.

We may conclude, therefore, that bile must be present in the intestine for phenolphthalein to have a marked cathartic action. Catharsis from phenolphthalein is nearly always absent in obstructive jaundice. It is generally present in non-obstructive jaundice.

Urinary Elimination of Phenolphthalein in the Jaundiced. In view of this absence of marked cathartic action in the jaundiced and the fact that bile is by far the best solvent that phenolphthalein meets in the gastro-intestinal tract, one might assume that phenolphthalein is not dissolved in the jaundiced as it is in the normal individual. To determine whether this was the case, we made careful quantitative observations upon the elimination of phenolphthalein in the urine. Much to our surprise, we found that, if we consider the phenolphthalein elimination in the urine an index of its solution and absorption—and there is reason to believe that it may be—the jaundiced patient absorbs phenolphthalein. This is shown by Tables 1 to 3 as well as by Graphs 1 to 3.

It was found in a previous study^{2b} that the total percentage of

the dose of phenolphthalein eliminated in the urine of normal individuals ranged from 1.41 to 19.7%. In jaundiced patients, we find that the elimination percentage varies from 0.97 to 19.1% of the quantity ingested. The fact that these figures are practically identical is all the more remarkable as the jaundiced patients received much larger dosage than the normal individuals previously studied.



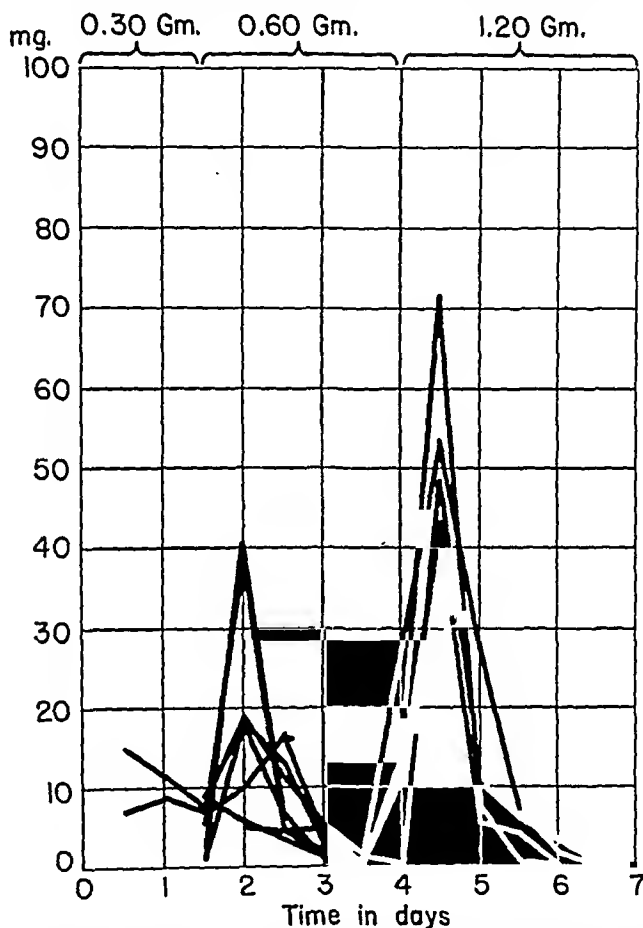
GRAPH 1.—*Proved Obstructive Jaundice*: Total phenolphthalein elimination curve (composite) after 0.60 Gm. and 1.2 Gm. of phenolphthalein.

In the previous study we found that, for the normal individual who had cathartic effect from the dose, the elimination of phenolphthalein was practically at an end by the fourth day, while in individuals that had no cathartic action from the dose, the elimination time may be doubled. The peak of the elimination in the normal individual was reached on the first day in 44% of the cases and on the second day in 52% of the cases. On the third day the peak occurred in only 4% of the cases and never beyond that time.

Graphs 1 to 3 show that in some of the jaundice cases elimination continued for as long as 8 days, although for the majority of jaundiced individuals it came to an end about the fourth day. The

peak of elimination was reached on the first day in 24% of cases, on the second day in 74% of cases, and on the third day in 2% of cases.

What is particularly remarkable in these results is not only that the shape of the curves is practically identical, but also that their height is proportionate to dosage, *i. e.*, in general the peak is 10 times as high with the 600 mg. dose in the jaundiced patient as that resulting from the 60 mg. dose in the normal individual.



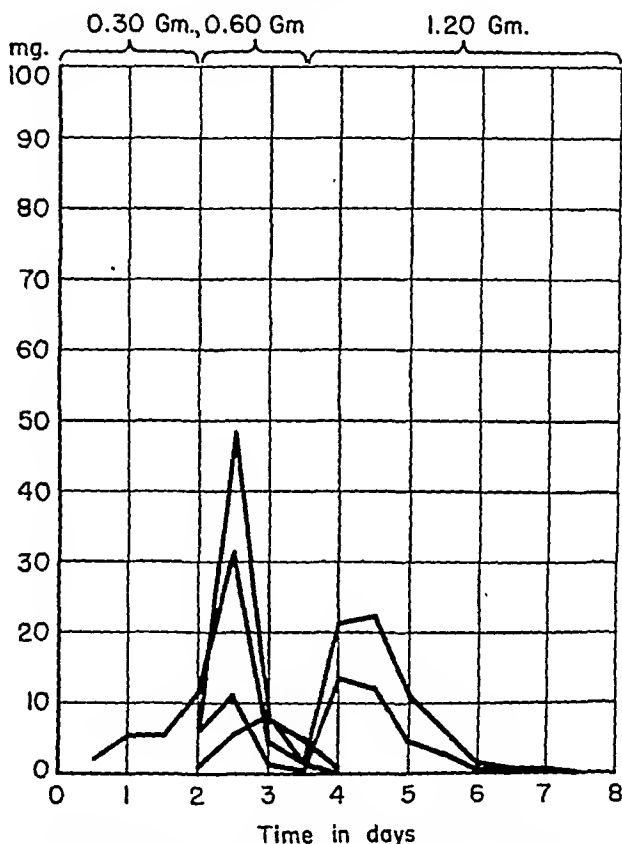
GRAPH 2.—*Probable Obstructive Jaundice*: Total phenolphthalein elimination curve (composite) after 0.30 Gm., 0.60 Gm., and 1.20 Gm. phenolphthalein.

CONCLUSIONS. *The elimination of phenolphthalein in the urine of the jaundiced patient is practically identical with that of the normal individual.*

Experimental Obstructive Jaundice. Since, in human obstructive jaundice, there is usually the complicating factor of inflammation or of other coexisting pathologic condition, it was deemed desirable to determine the action of phenolphthalein on previously susceptible cats that were rendered jaundiced by ligation of the common bile duct.

Method of Experimental Study. Adult cats were tested for their susceptibility to phenolphthalein by the administration of 4 gm. per kg. of the drug, this dosage having been previously determined as the amount that would always result in a liquid stool in a cat susceptible to the action of the drug. Only those cats that were found to be susceptible to this dose were subjected to operation.

Under ether anesthesia, the gall bladder and bile ducts were exposed by a right rectus incision, the bile ducts were ligated both at the confluence with the pancreatic duct and at the bifurcation of the hepatic duct. The intermediate portion was excised. When care was taken completely to



GRAPH 3.—*Hepatositis Jaundice*: Total phenolphthalein elimination curve (composite) after 0.30 Gm., 0.60 Gm., and 1.20 Gm. of phenolphthalein.

occlude all branches of the bile ducts (the cat appears to have more than one), the cat became icteric and showed bile pigment in the urine within about 3 days. At the same time the stools became clay-colored and an examination of the stool for hydrobilirubin was negative.

Cats with experimental obstructive jaundice live in good health for about 3 weeks and accept their food, which in this study consisted of milk and ground meat. They then refuse to eat, a low-grade upper respiratory infection develops along with alopecia and a scaliness of the skin. Death usually takes place in from 4 to 6 weeks following operation. Autopsy shows a deep greenish discoloration of the intestines, mesentery and omen-

tum and a generalized wasting with pigmentation of all the tissues. In all instances there has been a great dilatation of the gall bladder and of the stump of the common bile duct, as well as of the cystic duct. In 1 instance, 1 month after the induction of the obstruction, the dilated organ contained 50 cc. of bile. In another instance the gall bladder ruptured spontaneously and a bile peritonitis resulted. The wall of the gall bladder shows, on histologic examination, a marked hypertrophy of the mucosa and submucosa and some increase in the muscularis.

In no case during this study have we observed ascites or dependent edema as was found in the case of dogs with obstructive jaundice by Still and Carlson.⁴

One week after operation, when the cat had fully recovered from the immediate effects, a dose of 4 gm. of phenolphthalein per kg. body weight was administered. One week later this dose was repeated; and again at intervals of a week until the cat was sacrificed or died.

Results. Nine cats with artificially induced obstructive jaundice, who previous to operation had been found susceptible to phenolphthalein administration, were entirely negative as to cathartic action after obstruction of the bile ducts was produced. In most instances these animals passed acholic formed stools, which consisted largely of solid lumps of unaltered phenolphthalein. In 1 susceptible animal, operated on *unsuccessfully* as to production of jaundice, the administration of phenolphthalein resulted in catharsis. This proves that the operative procedure itself was not responsible for the refractoriness of the jaundiced animals. The absence of cathartic effect in these animals is fully confirmatory of the results obtained in human obstructive jaundice.

CONCLUSION. *In experimentally induced obstructive jaundice in cats, the previously effective dose of phenolphthalein loses its cathartic action.*

Excretion in Bile of Humans. The fact that phenolphthalein, though absorbed from the bowel, is inactive as a cathartic in individuals with obstructive jaundice makes plain the great importance of bile in activating phenolphthalein. In the further study of the mechanism of phenolphthalein action, it seemed necessary next to study the elimination of phenolphthalein in the bile. Facilities for such direct study were found in the surgical wards of the Cook County Hospital, where one can usually encounter one or more patients who have a draining gall bladder or common bile duct, and who are generally also in need of cathartic action for therapeutic reasons.

Procedure. Both jaundiced and non-jaundiced bile fistula patients were subjected to this study, the latter as controls. The total quantity of urine and bile excreted in 24 hours was collected preliminarily and tested for the presence of phenolphthalein. After determining the absence of phenolphthalein from both urine and bile, each patient was given 0.6 gm. of phenolphthalein orally, and the 24 hours' collection of specimens was continued. The daily 24-hour specimens were measured and the presence and amount of phenolphthalein in each of them was determined. Some 20 to 24 hours after the intake of phenolphthalein, 10 cc. of blood were drawn

and the serum tested for phenolphthalein. The daily quantitative and qualitative determinations of phenolphthalein in the bile and urine were continued until no phenolphthalein was demonstrable.

Results. To date 12 cases were studied with 13 determinations. Of these, 6 patients were icteric and 5 non-icteric; and 1, Case J-7* at first jaundiced, was later placed in the non-icteric group. *The surprising and unexpected finding in this study was the small amount of phenolphthalein (average 0.18%) or even its absence—both free and conjugated—from the bile of the jaundiced patients, as shown by Table 4 and in Graph 4.* The urinary elimination of phenolphthalein

TABLE 4.—PHENOLPHTHALEIN EXCRETION IN HUMAN FISTULA BILE.

Phenolphthalein eliminated.					
Case.	Urine.		Bile.		Grand total.
	Free.	Total.	Free.	Total.	
<i>Jaundiced:</i>					
J-1	0.433	4.683	0.0	0.016	4.70
J-2	0.78	4.11	0.0	0.0075	4.118
J-3	0.44	10.074	0.02	0.25	10.324
J-4	0.95	5.01	0.0	0.0	5.01
J-5	1.90	10.19	0.06	0.073	10.263
J-6	1.29	4.96	0.03	0.717	5.677
Average . .	0.96	6.50	0.019	0.18	6.68
<i>Not jaundiced:</i>					
N-1	0.19	1.59	0.0	2.18	3.77
N-2	0.09	3.93	1.01	1.76	5.69
N-3	0.43	5.21	3.43	4.28	9.49
N-4	0.525	2.29	2.72	3.37	5.66
(2d dose) . .	0.488	2.66	4.693	5.52	8.18
N-5	8.15	24.13	2.28	3.75	27.88
Average . .	1.31	6.63	2.35	3.47	10.11

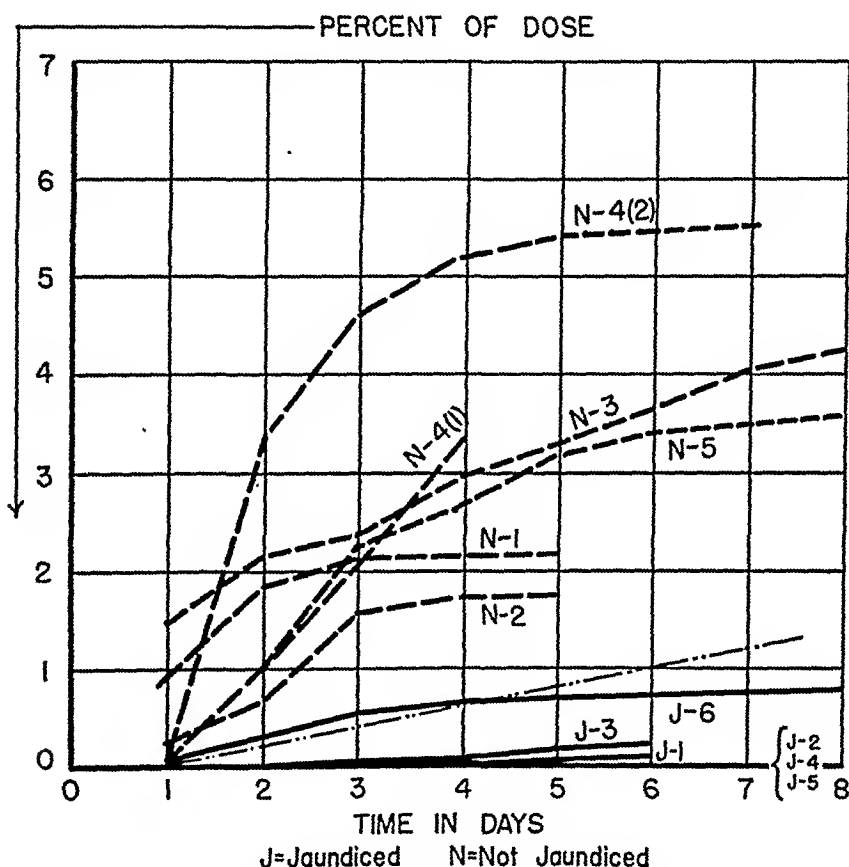
In the jaundiced patient the fistula bile is almost free from phenolphthalein in any form. The fistula bile of non-jaundiced patients contains both free and conjugated phenolphthalein. The urinary elimination in both groups is the same.

(average in jaundice cases 6.5% and in non-jaundiced cases 6.63%) is shown in Graph 5, from which it will be seen that the jaundiced patients eliminated as much phenolphthalein in the urine as the

* Patient J-7, who presented very exceptional findings, was not included in the tabulation. This patient entered the hospital with a moderately severe jaundice and a diagnosis of cholelithiasis was made on a basis of an icterus index of 68 and the history and clinical findings. While under observation, the jaundice decreased progressively and, when the patient was subjected to operation, the icterus had almost disappeared. Hence this patient, although classed in the jaundice group, was almost completely free from jaundice when the fistula bile studies were begun. The output of bile through the drainage tube was exceptionally large—much greater than in any of the other cases, normal or jaundiced. Her average daily output during 11 days was 530 cc. per day, in comparison with the next highest average, which was 400 cc., and the lowest daily average of 60 cc. per day. The output of bile in this case on some days reached a total of 900 cc. The findings were as follows:

Total phenolphthalein eliminated was 28.67% of the dose ingested. Of this, 3.05% was eliminated in the urine, 1.33% being free; and 25.62% was eliminated in the bile, 5.13% being free. From this it will be seen that though she had been jaundiced, this patient had recovered sufficiently actually to belong to the non-jaundice group.

non-jaundiced. Even though these jaundiced patients had no phenolphthalein in the bile, they had cathartic action from phenolphthalein administration as soon as bile appeared in the stool after operative removal of the obstruction. The blood, with the exception of 1 case with icterus, contained conjugated phenolphthalein in the jaundiced as well as in the non-jaundiced patients in practically the same amounts; but no free phenolphthalein (excepting occasionally a trace).

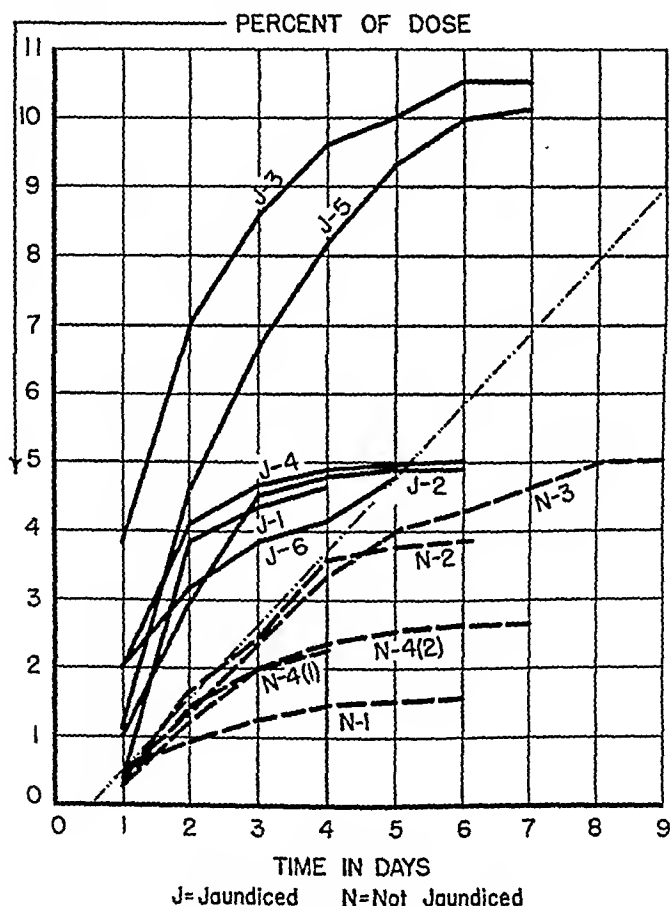


GRAPH 4.—Elimination of total phenolphthalein in fistula bile.

Tetraiodophenolphthalein Tests. The observation that in jaundiced patients the bile fails to contain any appreciable amount of phenolphthalein led us to try the same test with sodium tetraiodophenolphthalein, the dye used in gall-bladder visualizations. This was given to 4 patients in accordance with the usual routine for the Graham-Cole test, and the bile was then examined for its content of the dye. The bile of the non-jaundiced patients contained a substance which gave a phenolphthalein-like reaction, while that of the jaundiced did not give such a reaction. Although only 4 cases could be checked thus far, it appears that the results coincide with those secured with phenolphthalein. This observation definitely

coincides with the general clinical experience that the Graham-Cole test is of little value in jaundiced patients as it is nearly always negative in them.

Excretion in Cat Bile. A study of the bile content in phenolphthalein of normal and of jaundiced cats was also undertaken. The bile was taken within 24 hours after the administration of 4 gm. of phenolphthalein per kg.; and it was again found, as is shown in Table 5, that the bile of the jaundiced animals contained only minimal quantities of phenolphthalein; averaging approximately one-hundredth of that contained in the bile of normal animals given the same quantity of phenolphthalein.



GRAPH 5.—Elimination of total phenolphthalein in urine.

CONCLUSION. *The bile of jaundiced patients and of cats with experimentally induced jaundice contains little or no free phenolphthalein and a very small amount of conjugated phenolphthalein.*

There seems to be an inverse ratio between the degree of jaundice and the quantity of phenolphthalein excreted in the bile.

TABLE 5.—PHENOLPHTHALEIN EXCRETION IN CAT'S BILE.

A. Bile of Normal Cats.

Cat.	Free phenolphthalein, mg. %.	Conjugated phenolphthalein, mg. %.
F-5	0.2	130
J-21	0.3	255
J-22	0.2	150
4-1	0.3	170
4-2	0.3	250
4-3	0.3	100

B. Bile of Jaundiced Cats.

Average	0.3	176
J-1	0	0.2
J-2	0	0.15
J-3	6.2	4.3
J-31	0.2	2.5
Average		1.78

Elimination of free and of conjugated phenolphthalein in the bile of normal cats (A) and of jaundiced cats (B) given 4 gm. of phenolphthalein per kg. Phenolphthalein is present in about 100th the amount (averaged) in the bile of the jaundiced animals.

TABLE 6.—GALACTOSE TOLERANCE TESTS IN JAUNDICED PATIENTS BEFORE AND AFTER THE GIVING OF PHENOLPHTHALEIN.

No.	Name.	Diagnosis.	Icterus index.	Galactose excretion in gm.		Result.
				Before Phtn.	After Phtn.	
1	J. M.	Catarrhal jaundice	140	3.60	2.90	Improved Home
			100	2.70	
			45			
2	J. F.	Catarrhal jaundice	225	2.60	2.50	Home
			90			
			55			
			22			
3	S. N.	Cholelithiasis	62	1.90	1.80	Home
			55			
			38			
			95			
4	E. S.	Cholelithiasis	115	2.30	2.30	Home
			46			
			35			
			75			
5	A. S.	Cirrhosis	15	2.40	2.40	Home
			100			
6	J. W.	Cirrhosis	94	2.50	2.80	Home
			74			
7	C. H.	Choledocholithiasis	37	1.30	1.40	Laparotomy Died
			112			
			45			
8	F. K.	Ca. of head of pancreas	50	1.90	2.20	Laparotomy Died
			63			
			86			

There is no increased galactose elimination in the urine that can be ascribed to the administration of phenolphthalein,

Liver Function Tests. While conducting these studies, we undertook a few galactose tolerance tests upon jaundiced patients before and after the taking of the phenolphthalein. Though the series is small, the results are nevertheless reported as case abstracts as well as in Table 6.

From these observations it will be seen that there has been no impairment in galactose tolerance that could in any way be ascribed to the phenolphthalein, even when taken in large (1.2 gm.) doses. In the few cases in which increase in galactose elimination did occur, the deterioration of liver function was directly ascribable to the patient's condition, most especially the operation.

CONCLUSION. *In a limited number of cases of jaundice, the galactose tolerance tests showed no impairment of liver function ascribable to phenolphthalein.*

Discussion. We have shown that individuals suffering from obstructive jaundice, in whom there is no bile in the bowel, are acted upon by phenolphthalein little or not at all, even when it is given in large doses. Some of these very individuals who had no evacuant action from phenolphthalein during the time that their stools were acholic reacted to phenolphthalein in the normal manner by cathartic effect as soon as bile was present in the bowel. These observations have been verified on experimentally jaundiced cats.

We also find that phenolphthalein is eliminated in the urine of jaundiced individuals to the same extent and in the same manner as in normal individuals.

We then face the remarkable fact that, while phenolphthalein is presumably absorbed and therefore dissolved in the bowel, it fails to act in the former if bile is absent in the bowel.

The fact that patients who are suffering from jaundice due to degeneration of liver parenchyma (hepatosis jaundice) and who have bile in the stool have reacted to phenolphthalein in about the same way as normal individuals, again shows the importance of bile to the action of phenolphthalein.

We must, therefore, postulate that either bile activates the phenolphthalein in the bowel or else it is activated as it passes through the liver and is eliminated in the bile. This latter postulate is answered in the negative by the finding that phenolphthalein is not present or is present only in small amounts in the bile of jaundiced patients. Though the number of cases studied thus far is relatively small, the results are so constant and definite as to be conclusive, especially as the same results were consistently noted in the experimentally jaundiced cats. The facts found are tabulated in Table 7.

TABLE 7.—PHENOLPHTHALEIN IN THE JAUNDICED AND NON-JAUNDICED.

	Jaundiced.	Non-jaundiced.
Catharsis	0	+
Conj. in urine	+	+
Conj. in bile	0	+

Now it is a fact that patients who are jaundiced and do not excrete phenolphthalein in the bile have cathartic action from the phenolphthalein, providing bile enters the bowel. This proves conclusively that *it must be an action of the bile in the bowel on the phenolphthalein* or a joint action of the two that is responsible for producing the effect upon the intestine necessary for the production of the cathartic action.

The presence of conjugated phenolphthalein in the blood serum of jaundiced patients and of an abundance of conjugated phenolphthalein in the urine of the jaundiced points to the conclusion that conjugation of phenolphthalein still occurs in the system in spite of the fact that the liver is diseased, as evidenced by the jaundice. Numerous theoretic questions crowd one's mind as to the interpretation of these phenomena. Is the liver of the jaundiced patient still a seat of the conjugation of this water-soluble body (*i. e.*, the conjugated phenolphthalein)? Even if it is not, why should the liver fail to eliminate the water-soluble conjugated phenolphthalein when the kidney is capable of doing so and the normal liver does this to so much greater an extent than the kidney? The significance of this remarkable finding remains to be investigated. The question may also be asked: what is the fate of the phenolphthalein that is not eliminated through the bile in the jaundiced individual, as no excess is eliminated in the urine?

Conclusion. 1. The presence of bile in the bowel is necessary for the cathartic action of phenolphthalein in man, as there is no such effect or very little of it in cases of obstructive jaundice. On the other hand, phenolphthalein is generally active in jaundiced patients who have bile in their stools.

2. Phenolphthalein is not suitable as a cathartic in individuals suffering from obstructive jaundice and whose stools are completely acholic.

3. Cats that have been found susceptible to the cathartic action of phenolphthalein lose this susceptibility upon being subjected to experimental obstructive jaundice.

4. The cathartic action of phenolphthalein is evidently due to a local effect of bile upon the phenolphthalein in the bowel.

5. Even though it does not act as a cathartic in individuals with obstructive jaundice, it is eliminated in the urine to the same extent as in the normal individual.

6. Phenolphthalein, chiefly in its conjugated form, is eliminated in large quantities in the bile of normal individuals. Free and conjugated phenolphthalein are present in but minute amounts in the bile of the jaundiced.

7. No evidence of phenolphthalein produced liver damage has been found in these studies, as far as the galactose tolerance test, performed in a few cases, could show.

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CHRONIC HYPOGLYCEMIA.

A PROBLEM IN CARBOHYDRATE METABOLISM.

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SHORTLY after the World War there came from Germany a series of reports describing the favorable reactions of many malnourished patients during treatment with continued small doses of insulin. The blockade had accomplished its purpose and the fall of 1918 found a large part of the civilian population of Germany in a condition of enforced semistarvation. Returned to a more normal diet, many of those individuals exhibited a curious phenomenon. They were unable to eat and hence unable to regain weight. Underfed for many months, certain metabolic readjustments occurred which, in some instances, obtained after an apparently adequate caloric supply was available. In the management of such cases insulin was of definite benefit and its use was followed by increased appetite, gain in weight and increased body tone in general.

These results excited interest in this country and a wave of enthusiasm swept our clinics which led to the widespread use of insulin in the treatment of many types of patients who exhibited one symptom in common: They were all underweight. Early reports were most favorable; but as months passed it became obvious that only a limited number of the underweight responded to insulin therapy and such a favorable response could not be predicted. The initial enthusiasm waned and, due to repeated failures, the treatment fell into discredit in many clinics.

Our experience at the Cincinnati General Hospital was similar to that of many others. Some patients showed remarkable improvement, but many remained entirely refractory to treatment or at

best gained weight for a few weeks and then relapsed. These circumstances stimulated us to investigate the carbohydrate metabolism of our patients who were underweight, in hopes that we might find some factor which would serve to set apart those who improved from the ones who did not. Unable to find any such study in the literature, we decided to begin by recording the glucose tolerance curves of our malnourished patients.

Early in the experiment it became obvious that these people fell into two distinct groups. The first group showed what is universally accepted as a normal glucose tolerance curve (Fig. 1) with a rise of 80 to 140 mg. % above the fasting level after the administration of glucose and a rapid drop to a figure slightly below the fasting level between $2\frac{1}{2}$ and 3 hours, then a subsequent rise to the fasting level.

The second group was characterized by a curious and unexpected curve (Figs. 3, 4, 6, 9, 13, 14, 16, 17). In these curves it will be apparent that the fasting level is within normal limits, though usually at its lower range, and the blood sugar fails to rise, even to the upper limits of the fasting level after the administration of 100 gm. of glucose by mouth. This low curve remains between 80 and 100 mg. % throughout the 3 hours after ingestion of the sugar. Such curves are adequately represented by the simple graphs and require no further description. Similar flat curves have previously been described, occurring in certain patients with hypothyroidism and in some with pituitary disturbances. We have failed to find any relation between our flat curves and the basal metabolic rates and their incidence of frequency is many times that of recognized pituitary disease, though it is not at all impossible that some functional pituitary disturbance is related to the syndrome. It is significant to state, at this point, that we found over 70 individuals who showed low curves in the first 18 months of our study and that they were selected from the ambulatory thin patients coming to the out-patient department.

For these we have chosen the designation, chronic hypoglycemia. However, they must be differentiated from patients with spontaneous hyperinsulinism, for some investigators have described this latter group under the term chronic hypoglycemia,⁶ although the name is not an apt one. In spontaneous hyperinsulinism the glucose tolerance curve does not remain in the low fasting zone throughout the test, but instead it is characterized by a sharp initial rise during the first 30 to 45 minutes after ingestion of glucose. This is illustrated in Figure 2, where the blood glucose reaches 230 mg. % 30 minutes after feeding. This abrupt rise is then followed by a marked exaggeration of the normal fall, in the case represented by Figure 2 falling to 45 mg. % after $2\frac{1}{2}$ hours, with the appearance of the usual signs of insulin shock at the point marked X on the

graph. At this time it was necessary to administer glucose and orange juice to control the symptoms. Thus, in hyperinsulinism there are points on the curve where the blood glucose drops into the hypoglycemic zone, but this fall represents an exaggerated insulin response to the normal increase in blood glucose after ingestion of carbohydrate. So, in Figure 2, we find a spread of 290 mg. % between the high and low points on the curve, while in chronic hypoglycemia the total spread is usually less than 25 mg. %. The syndrome of chronic hyperinsulinism has been ably set forth by Harris^{4a} and we emphasize the difference between the two conditions at such length only because we know that the differentiation has not been appreciated and the two conditions are frequently confused in the literature dealing with the subject.^{2a}

Having learned that individuals who are underweight fall into two groups with respect to their response to carbohydrate feeding, we wished to know whether this difference might be related to the variation in response to insulin therapy. We were alarmed at the idea of giving insulin to persons whose blood sugar remained at such low level as those demonstrated in Group 2 and decided to try insulin therapy in the first group, those whose sugar curves were normal. We felt that, at least, we could do them no harm. We selected a group of such patients (*e. g.*, Case E. S., Fig. 5) who were given insulin in doses of 5 units before breakfast, 10 units before lunch and 10 units before dinner. This was administered 15 minutes before meals and they were permitted to select their own dietary. The results were disappointing and after some weeks it became obvious that such persons would not gain weight under our treatment. When we examined the individuals comprising the group more carefully, certain facts became apparent. For the most part these people did not complain of poor appetite; instead they were the well-known thin individuals who eat 2500 to 4000 Calories a day by choice, and still do not gain weight. They, with few exceptions, were of the wiry type of leanness, with good muscle tone and good nervous tone. There were few neurotics in the group and, in short, they may be described as representatives of the sthenic type of thinness.^{2b}

We then compared the individuals in Group 2, those showing the flat curves, with Group 1. Not only did their sugar tolerance curves differ but, as a class, they exhibited other distinctive differences. They had poor appetites and food did not interest them. They were nervous and irritable, with insomnia, excessive fatigue on exertion and general apathy as outstanding symptoms. In many instances the stigmata of neurasthenia were obvious. They represented the asthenic type of thinness.

With considerable hesitation, due to fear that we might force an already low blood sugar into the danger zone, we repeated the same

experiment, using a few patients from the second group. No ill-results followed and within a few weeks there was noticeable improvement. The first change was a disappearance of anorexia; they began to eat and soon to gain in weight. As appetite and weight improved, nervousness, irritability and asthenia disappeared and, accompanying this improvement, the glucose tolerance curves rose into the normal range. When after 2 or 3 months insulin was withdrawn abruptly, a gradual return of the subjective symptoms occurred, they lost weight and the blood sugar curve resumed its previous flat configuration. When, however, the administration of insulin was continued over a longer period of time, 6 months or more, and then was withdrawn slowly (reducing the dose from 3 times daily to twice and then once daily) some of these patients have maintained their improvement in both its clinical and chemical aspects for many months. One might surmise that insulin, either directly or indirectly, had brought about a readjustment of some abnormal metabolic deviation. We may illustrate these facts most concisely with a few selected cases represented in the graphs.

Case Reports. CASE 1.—(Figs. 6, 7 and 8 illustrate a typical response.) The patient had for many years been decidedly underweight. When first admitted to the hospital he weighed only 122 pounds, though he was almost 6 feet in height. His outstanding subjective symptoms were undue fatigue on exertion and loss of appetite. He had previously been suspected of having either tuberculosis or hyperthyroidism, but adequate studies had ruled out both of these probabilities. He had been subjected to a 3 months' period of rest and high caloric feeding without substantial improvement. The initial sugar tolerance curve is represented in Figure 6 and shows the characteristic flat configuration. After 8 weeks of insulin treatment he had gained 6 pounds and his blood sugar curve showed marked improvement (Fig. 7). Six months after treatment began he had gained 12 pounds in weight and his curve was entirely normal. There had been marked subjective improvement in all of his symptoms and he was able to carry on the day's work without undue fatigue. Insulin was gradually withdrawn and his improvement continued.

CASE 2.—(Represented in Figs. 9 to 12.) This patient had been a problem case under observation in the out-patient department for 3 years before our experiment was started. Throughout that time her weight had varied between 86 and 90 pounds. Her expected weight was 108 pounds as given in actuary statistics. Subjective symptoms were anorexia, asthenia, marked "nervousness" and insomnia. Again, as in the first case, both tuberculosis and hyperthyroidism were suspected early in the course of observation but neither diagnosis could be established. She had been admitted to the hospital for a month of bed rest combined with high caloric diet. During this period of hospitalization she gained in weight from 84 to 90 pounds, and this gain was lost within the 3 weeks following her discharge. On her return to the dispensary, the fruitless struggle was resumed with "tonics," vitamin concentrates, and sedatives and she was recognized as one of those undernourished neurotics who haunt every clinic. Figure 9 shows her flat sugar tolerance curve at the end of 3 years as our patient. When we began insulin treatment her weight was 88 pounds.

After 6 months of insulin in doses of 8-10-10, and on a diet of her own choice, her weight had increased 14 pounds, and her blood sugar curve (Fig. 10) was quite normal. She no longer required sedatives, was eating almost 3000 calories a day and said she was "feeling better" than she could remember in many years.

At this point insulin was stopped abruptly and for 2 months the improvement continued and her gain in weight held. Then, gradually at first, but with increasing rapidity she relapsed into her former state, and after 3 months without insulin began to lose weight rapidly. The glucose tolerance curve at this time (Fig. 11) showed a striking change from the one illustrated in Figure 10 and indicates the reversal in the type of curve which was associated with the recurrence of clinical symptoms. Insulin therapy was resumed and again there was prompt response so that 8 weeks later she weighed 104 pounds, or 16 pounds more than her weight at the beginning of the experiment almost a year before. Figure 12 shows her normal glucose tolerance curve at the end of that time when her subjective symptoms had largely disappeared. Insulin was then slowly withdrawn and her improvement has been sustained.

In searching for some explanation for this apparently paradoxical action of insulin, it is obvious that the question of carbohydrate absorption from the intestinal tract would present itself. Might some inhibition to the rate of sugar absorption explain the flat curves and was it possible that insulin acted to remove this inhibition? To answer this question we gave glucose to certain patients in the group under consideration by the intravenous route. There was no change in the characteristics of the tolerance curve; it remained the same flat curve regardless of the method of introducing carbohydrate. This fact is illustrated by Figures 13 and 14. In the first graph is shown the low flat curve after 100 gm. of glucose had been given by mouth, while Figure 13 represents the almost identical configuration following the intravenous administration of 40 gm. of glucose (40 gm. is the amount usually employed in intravenous tolerance test).

Neither method of giving glucose was followed by glycosuria in any patients with low curves, but it is of interest to note that transient glycosuria frequently occurred during insulin treatment as the blood sugar rose to normal levels. Thus some patients would spill sugar through the kidney at blood sugar ranges between 120 and 150 mg. % for a short time and then, as the blood sugar was maintained in the normal range, this glycosuria would disappear, suggesting that the renal threshold may vary with the habitual level of blood sugar.

We have been unable to establish any constant relationship between the low curves shown by these patients and the basal metabolic rate. This has interested us because, as already mentioned, the low glucose tolerance curve has been described in hypothyroidism. This absence of correlation is shown in the graphs. For example, the patient represented in Figure 3 with flat curve

had a basal metabolic rate of -20 , but another patient with a flat curve (Fig. 4) had a basal metabolic rate of $+4$. Other patients with flat curves (Figs. 6 and 9) had metabolic rates of $+6$ and $+13$ respectively. On the other hand, the patient identified by Figure 5 had a normal sugar tolerance curve and a basal metabolic rate of -33 . He was not helped by insulin but did improve when given thyroid extract.

In consideration of these facts the case represented in Figures 16, 17 and 18 interested us greatly. This patient had a low flat curve, a basal metabolic rate of -24 and clinical signs of mild hypothyroidism as revealed by changes in the hair and skin and increasing lethargy. Thyroid extract alone was given by mouth for 4 months and at the end of this period the clinical signs of hypothyroidism had disappeared, while the basal metabolic rate had risen to -6 . The glucose tolerance curve, however, remained in the low zone, showing if anything an exaggeration of the low level (Fig. 17). At this point thyroid extract was discontinued and insulin given in the usual manner. Six weeks later the tolerance curve had been elevated into the normal range while the basal metabolic rate remained at -4 (Fig. 18). It is interesting to note that the glucose tolerance curve persisted in the low zone after the basal metabolic rate had risen, but later, following insulin treatment, the curve showed a normal configuration.

Discussion. During a period of 18 months, 62 individuals who had low glucose tolerance curves were encountered among ambulatory patients seen in the clinic and private practice. It would seem that the existence of chronic hypoglycemia is far more common than is generally appreciated and that it frequently occurs in asthenic undernourished individuals who present the familiar picture of the "effort syndrome." We believe that the constantly low level of blood sugar may be, in part at least, responsible for the lack of vigor which characterizes these people, since the chief source of energy in mammalian metabolism is derived from the burning of carbohydrate. Patients with chronic hypoglycemia show a glucose tolerance curve which remains in the fasting zone regardless of the ingestion of food and it is possible that under these conditions there is inadequate fuel to be suddenly expended in the form of energy.

This syndrome must be differentiated from spontaneous hyperinsulinism for in the latter the hypoglycemia is cyclic, appearing in recurring episodes during which the blood sugar falls to dangerously low levels (60 mg. % or lower). John⁵ has suggested the treatment of hyperinsulinism with small doses of insulin but we have found that this condition is exaggerated by insulin and other investigators have confirmed this finding.³ It is possible that John was not dealing with true hyperinsulinism in his cases which responded favorably to insulin therapy but with the condition which we have

described. As we have demonstrated, many of our patients have improved on insulin treatment, but we would not leave the impression that favorable results have always followed. Some have tolerated insulin well without any change in their clinical symptoms but a few have not tolerated this treatment. It may be that our arbitrary dose of insulin was too large for the individuals in this second group and we are reinvestigating their reactions using much smaller amounts. Fifteen patients treated with insulin for 6 months or longer showed marked improvement, 4 failed to improve and 3 reacted unfavorably, showing the symptoms of mild insulin reaction.

What is responsible for the low blood sugar level and how does insulin act to change this level? In order fully to understand our problem we must answer these two questions and at present we have no answers. We may, however, indicate certain avenues of inquiry which have suggested themselves during our work. We have given these people relatively large amounts of sugar. It has not been lost through the kidneys and has not been reflected in a rising blood sugar. What has happened to it? We have already eliminated the most obvious explanation, that it is not absorbed from the alimentary tract, by our experiments in introducing sugar by intravenous injection.

Consideration of the opening paragraph of this paper suggests another explanation. Prolonged semistarvation might result in the utilization of the carbohydrate stores in the body in liver and muscles, to be followed by a readjustment in metabolism resembling that in hibernating animals. Such a readjustment might account for loss of appetite when an adequate diet was made available. Under these conditions sugar, when given, would be taken out of the blood stream by the depleted liver and muscles as soon as it appeared. This reasoning may apply to the German patients, but it imposes a set of conditions which do not obtain in ours. An adequate diet has been available in the great majority of cases, and the failure to eat resulted entirely from loss of appetite. This loss of appetite is an intimate part of the syndrome and must be explained. Merely to state that insulin stimulated appetite and that such people improved when they ate, falls short of being an explanation. Further, it will be remembered that enforced caloric intake, in the absence of insulin, did not result in clinical improvement. In fact, certain observations throw doubt on the assumption that enforced starvation results in producing a flat sugar curve since one patient, studied in the advanced stage of starvation, resulting from organic obstruction in the esophagus, had a normal glucose tolerance curve. Harris⁴⁵ reports similar observations on 4 patients who were literally starving to death.

de Takats¹ has demonstrated that suprarenal denervation and splanchnic section on normal dogs results in increased storage and

fixation of glycogen in the liver. Apparently as a result of this increased storage and fixation, the blood sugar curve resembles the one we have described in spontaneous chronic hypoglycemia in humans. de Takats has suggested that under certain conditions of imbalance in the sympathetic nervous system a block occurs which inhibits the demobilization of hepatic glycogen and that such a block may be responsible for the clinical syndrome we have been studying. We have not found any method of demonstrating glycogen fixation in our patients.

At present we are carrying forward our investigation, studying the effect of the adrenalin demobilization action on hepatic glycogen, the hexosphosphate correlation and the blood phosphatase, in individuals showing low sugar curves. We must admit, however, that as yet we have no satisfactory answer to this peculiar problem in carbohydrate metabolism.

Summary. 1. Patients exhibiting a low, flat glucose tolerance curve are not infrequently encountered in this dispensary.

2. Most of these patients are underweight and present the clinical picture commonly described under such terms as neurocirculatory asthenia and effort syndrome.

3. This condition must be sharply differentiated from spontaneous hyperinsulinism, in which the glucose tolerance curve is not flat but is characterized by a marked exaggeration of the descending limb.

4. When treated with small doses of insulin a number of our patients with chronic hypoglycemia have shown marked clinical improvement, an increase in sense of well-being, gain in weight, and increased appetite, concomitant with this improvement the glucose tolerance curve returns to the usual normal configuration.

5. The precise action of the insulin in effecting this change is not at present understood. We suggest the possibility that the demobilization of hepatic glycogen is in some way inhibited and hope to establish this thesis by further investigation.

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DORST: CHRONIC HYPOGLYCEMIA

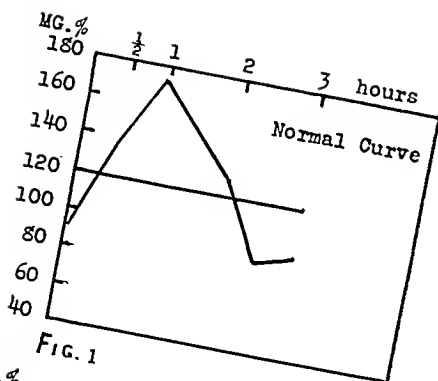


FIG. 1

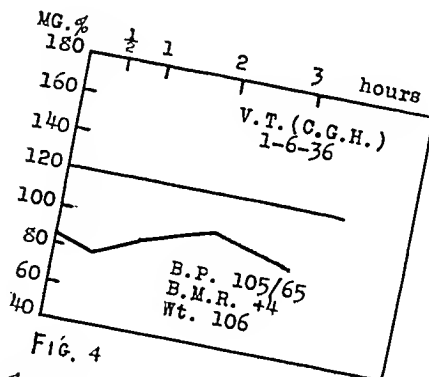


FIG. 4

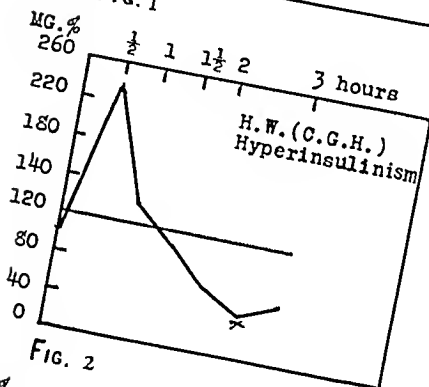


FIG. 2

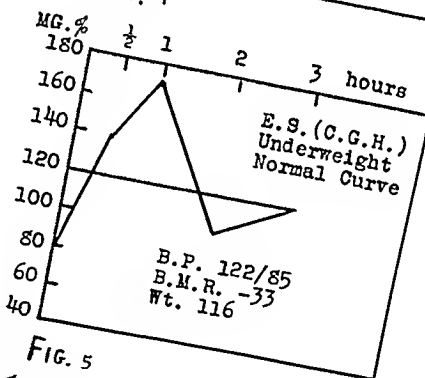


FIG. 5

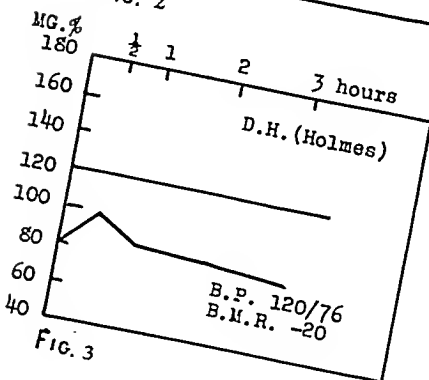


FIG. 3

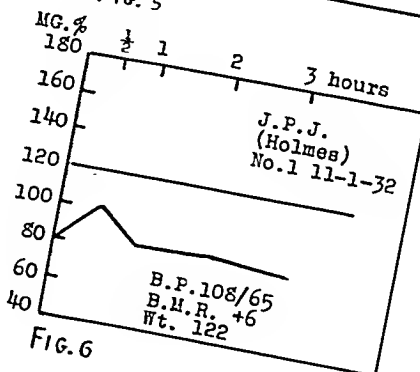


FIG. 6

FIGS. 1 to 6.

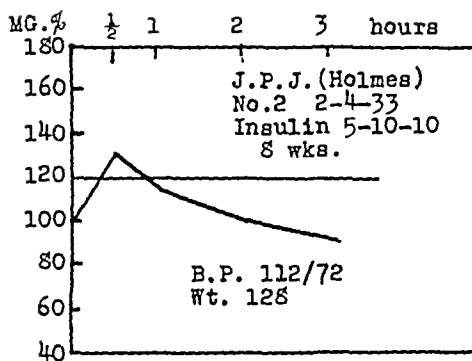


FIG. 7.

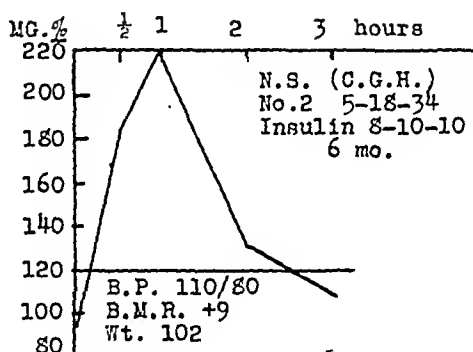


FIG. 10

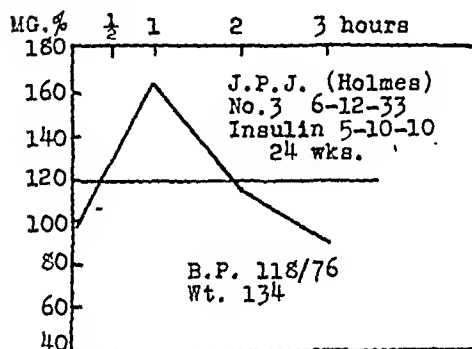


FIG. 8

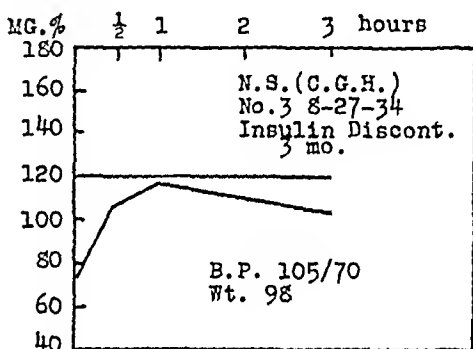


FIG. 11

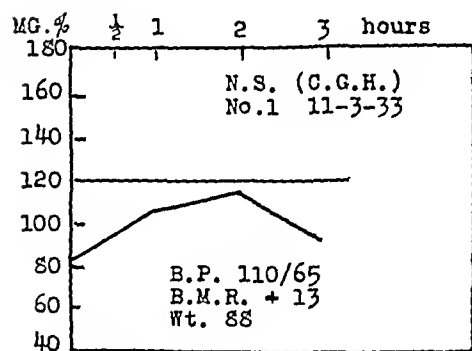


FIG. 9

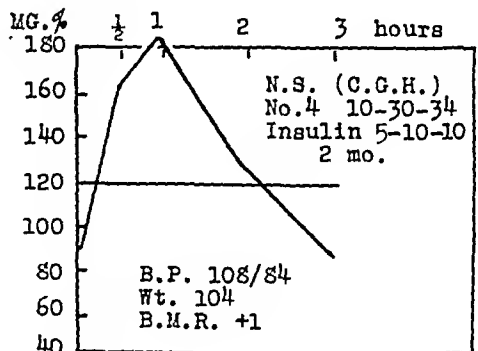


FIG. 12

FIGS. 7 to 12.

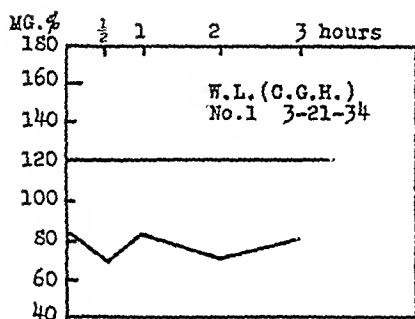


FIG. 13

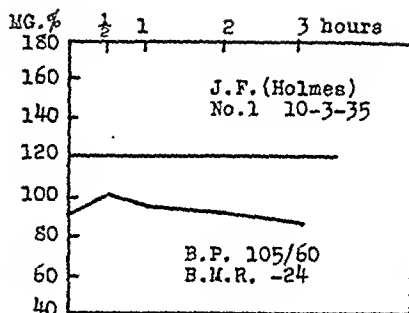


FIG. 16

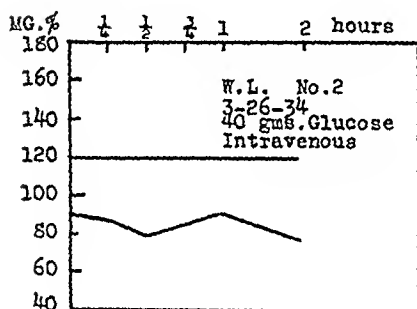


FIG. 14

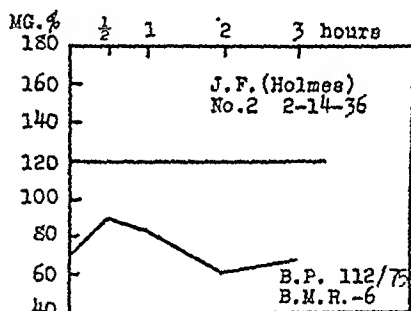


FIG. 17

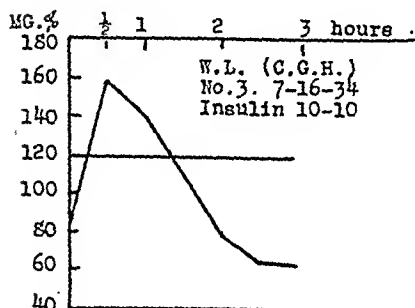


FIG. 15

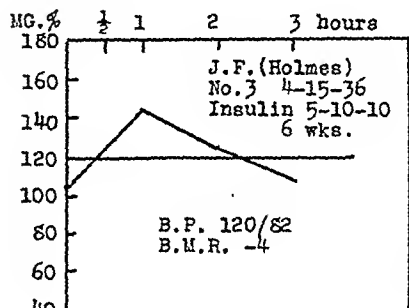


FIG. 18

PULMONARY PNEUMOCYST.

REPORT OF AN ENORMOUS SOLITARY CYST IN A HEALTHY
ADULT FEMALE.

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CYSTIC lesions of the lung may in general be divided into two main types: those containing fluid and those containing gaseous material, usually air. In the last few years, many examples of the latter type of disorder have been reported, often with the prefix "congenital."^{2-5,7} In recent months, certain authors⁶ have cast doubt on the *congenital* origin of many of these air-filled pulmonary cysts, and have subdivided such lesions into (a) congenital cysts and (b) acquired cysts of various types.

Serial examinations of patients recovering from various inflammatory disorders of the lungs, especially pneumonia, have revealed a surprising number of cases of bizarre cyst-like lesions. Many of these "cysts" or bullæ have undergone spontaneous resolution, but in some cases the change has remained stationary and in some it has even become progressive, finally involving an entire lobe or lung. These cases may easily be confused with partial or total pneumothorax. Having recently had the opportunity of seeing a remarkable case of massive pulmonary pneumocyst, in which, in spite of the presence of an enormous lesion, there was an almost complete absence of clinical symptoms, we are herewith placing it on record.

Terminology. The terminology of pulmonary pneumocyst is distinctly unfortunate. Strictly speaking, the word "pneumacele" (*pneuma*, air, and *cele* (xoilia), a cavity) is the most correct term; however, most of the literature to date refers to these lesions as cysts and it might cause confusion if a change were to be made at this time. Pierce and Dirkse⁶ use the term "pneumatocoele" which is as close to the correct one as any we have encountered. Ellison¹ misuses this word as synonymous with mediastinal hernia. Many physicians object to the word "cyst" on account of the lesions being non-fluid-filled, a reasonable objection.

Pathology. Koontz⁵ described two general types of cavities: bronchial dilatations and cavities resembling emphysematous blebs. Between these two extremes are all types of gradations. The cavities may or may not show communication with bronchi. In most cases the epithelium lining the cysts is columnar and ciliated, but it may be non-ciliated, cuboidal or flat.

The congenital lesions are said to lack pigment, thus differentiating them from the acquired type. The cysts may be single or multiple, unilocular or multilocular, and may vary in size from minute blebs to enormous sacs. They may contain air or fluid or both. The cysts may occur in any part of the lungs; in Koontz' series, both lungs were involved in one-quarter of the cases, the right lung alone in one-quarter, and the left lung in almost one-half. Males and females were affected about equally. Complications are rather unusual, but cases have been reported in which the cysts were associated with hydro- and pyothorax, pneumonia and even tuberculosis. Rarely, if fluid-containing, the contents may become purulent from secondary infection.

Many cases have no clinical symptoms whatsoever, and indeed most cases have been discovered incidentally in roentgenologic examination of the lungs.

Incidence. The incidence of really massive pulmonary pneumocysts is difficult to determine. They appear to be exceedingly rare. On the other hand, the reported cases of large pneumocysts are increasing in number, and, in our own observation, since we have been making routine postpneumonic chest Roentgenograms, we have seen several cases of medium-sized pneumocysts. We believe they occur in perhaps 20% of the cases recovering from pneumonia and represents a bullous emphysematous phase of healing. The *Quarterly Cumulative Index Medicus* lists approximately 70 different references to pulmonary cysts during the year 1937. None of these included any cases of massive pneumocyst.

Differential Diagnosis. The differential diagnosis of large pulmonary pneumocysts from pneumothorax is frequently quite difficult. In pneumothorax, the radiolucent shadow is often bordered on one side by the denser shadow of a collapsed lung, whereas in pulmonary pneumocyst this dense shadow is missing. In doubtful cases, a small diagnostic pneumothorax may reveal the thin wall of the cyst, but this procedure is not to be encouraged in cases with really large lesions, since the cyst may be accidentally entered and severe shock supervene. Serial Roentgen ray examination or comparison with previous films if available constitutes the most valuable method of diagnosis. Pneumothorax usually absorbs after a reasonable interval, while large pulmonary cysts may progress in size or remain stationary (Table 1).

Treatment. As long as the patient is symptomless, the treatment of pulmonary pneumocysts should be conservative. No giant air cyst should be tapped unless it interferes with respiration, because tapping of such cysts may be followed by shock and death.

Prognosis. The prognosis is quite uncertain, but is unquestionably good in the absence of complicating trauma or infection.

TABLE 1.—DIFFERENTIAL DIAGNOSIS BETWEEN CONGENITAL AND ACQUIRED CYSTIC PULMONARY DISEASE.

Acquired cystic disease.			
Congenital cystic disease.	(b) Bullous emphysema.		
	(a) Cystic bronchiectasis.	Moderate.	Massive.
	<i>Multiple</i>	<i>Usually multiple</i>	<i>Usually single</i>
1. Lesions may be <i>single</i> or <i>multiple</i>		May be <i>interstitial</i> or <i>peripheral</i> in location, the <i>interstitial</i> type especially simulating congenital cystic disease	May be <i>lobar</i> or may involve an <i>entire lung</i>
2. Often located in <i>middle third</i> of lung fields	Often <i>lobar</i> in distribution		<i>Thin-walled</i> or <i>no wall</i> at all visible
3. Lesion usually <i>thin-walled</i>	<i>Thin- and thick-walled</i>	<i>Thin-walled</i>	<i>Air filled</i>
4. <i>Air</i> or fluid filled or both	<i>Air and fluid</i> filled usually	<i>Air filled</i>	<i>No fibrosis</i> apparent (atelectatic lung stretched out parchment-thin around lesion)
5. <i>No fibrosis</i> in surrounding tissue	<i>Fibrosis</i> and pneumonitis in surrounding tissue	Some fibrosis in the <i>interstitial</i> type, often none in the <i>peripheral</i> type (fibrosis and/or lobular atelectasis)	Serial films or clinical evidence that lesion developed following pneumonia, etc.
6. Serial films since <i>infancy</i> show lesions	Serial films or clinical evidence that lesions developed following respiratory tract infection	Serial films or clinical evidence that lesions developed following pneumonia, asthma, etc.	Course variable; lesion may enlarge and embarrass respiration. Differentiated from pneumothorax by serial examination, clinical history and comparison with previous findings
7. Course benign; lesions usually persist or become worse except if infected	Course variable; lesions usually persist or become worse	Course benign; lesions may progress slowly or may rupture (spontaneous pneumothorax). "Acute" cysts may disappear rapidly, with little or no residual "scarring"	Coalescent alveolar or lobular ectasia. Pulmonary pneumatocele. Pulmonary pneumocyst. Large solitary pulmonary cyst
Synonyms: Congenital thoracic air cysts. Polycystic disease of the lung	Open honeycomb lung. Small generalized cysts	Localized alveolar or lobular ectasia. Central emphysematous bulla. Medium sized pulmonary cyst. Acute pulmonary pneumocyst. Chronic cystic disease. Polycystic lung	

Case Report. Miss V. B., a single, 19-year-old statistical worker, first came under our observation on May 12, 1937, because she had applied for a position with a company which required a routine medical examination for all new employees.

History. She stated she was perfectly well, although doctors had found some abnormal condition of her left chest since childhood which she called a hernia. She had had whooping cough and measles at the age of 4 years and chickenpox at the age of 10, but no illnesses since then. Her bowels were regular. The menses commenced at the age of 13 and had been regular since that time. She had just left junior college and was applying for her first position.

Physical Examination. Revealed a well-developed alert young woman weighing 121 pounds. Temperature, 36.8° C.; pulse, 86; respirations, 19. Inspection of the head and neck showed nothing unusual, except large cryptic tonsils and a deviation of the trachea to the right. There was a marked prominence of the upper chest. Only slight apical excursion occurred with respiration. The percussion note over the left chest was dull, while that over the right was hyperresonant. No breath sounds could be heard over the left lung except at the apex, where they were faint. The physical findings in the right lung were normal, except for the hyperresonance. No area of cardiac dullness could be made out on apex beat of the heart was felt in the fifth right intercostal space, 8 cm. from the mid-sternal line. No murmurs were present. Her abdomen was not unusual. The knee jerks were present and equal. The blood pressure was 150 systolic and 90 diastolic. Urinalysis was negative. The blood Kahn test was negative. The blood sedimentation rate was 5 mm. in 40 minutes and 10 mm. in 60 minutes.

Roentgen Examination. Roentgen examination reveals that the heart-vessel shadow is normal in size but is displaced a little over 5 cm. to the right; the trachea and mediastinum are similarly displaced, the maximum mediastinal "dislocation" being at the level of the sixth space posteriorly. There is moderate compression of the right lung. The left hemithorax is distended with either a very large pneumothorax or a very large cyst-like lesion. There is stretching out of the left diaphragm, with orthodox, though limited, movement. The right diaphragm appears normal. The esophagus is displaced to the right side along with the mediastinum but is otherwise normal. The cardiac end of the stomach is normal. Conclusion: Large left pneumothorax or pulmonary air cyst. The obvious absence of gross clinical symptoms on the part of the patient during Roentgen-ray examination and the absence of any history of recent sudden thoracic pain, thoracentesis or trauma, renders the diagnosis of massive pneumocyst the more probable.

(Subsequently, two previous films (August 28, 1928, and April 18, 1936) of the patient were secured for examination; these showed the cyst-like lesion to be almost unchanged (see illustrations).)

Additional Data. The patient's mother subsequently stated that the child was normal at birth. She contracted a cold at 2 years of age and a Roentgen ray of the chest was taken which showed an abnormal condition of the left lung. Some bulging of the upper chest was present then and has persisted since, although it has apparently not increased out of proportion to the child's development. Another chest Roentgen ray was taken at the age of 10 years and it was suggested she had an "upside down stomach." However, she seemed quite well and went through high school indulging in team volley ball, playing tennis, and swimming. She dances for a whole evening two or more times a week without difficulty. She never gets short of breath, except from prolonged exertion and does not

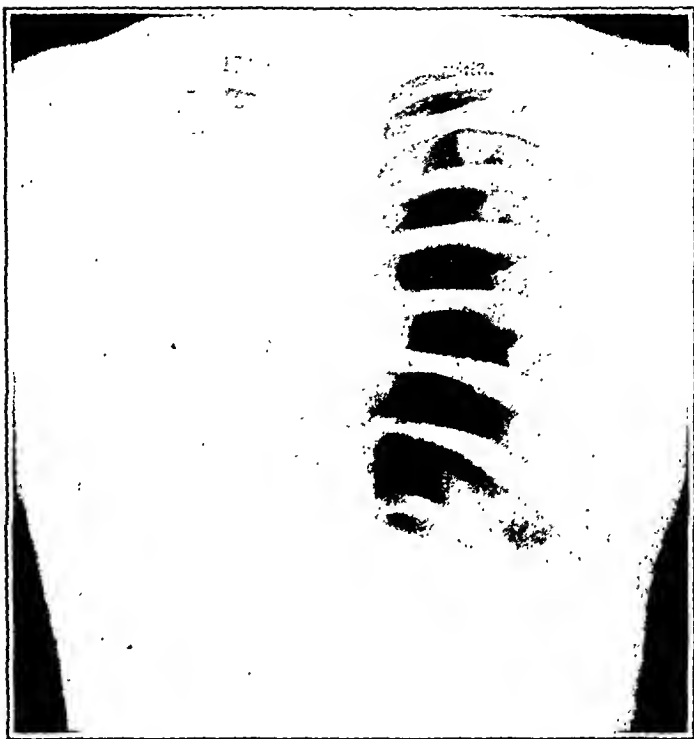


FIG. 1.—Postero-anterior chest roentgenogram made on 8/28/28. There is marked mediastinal and cardiovascular displacement to the right, with mediastinal hernia; compression of the right lung, principally of the right lower lobe; a large left pneumocyst, with flattening and stretching out of left half of diaphragm but no abnormality of the right half. (Note: This film was made by a previous consultant but the lesion was not diagnosed at the time.)

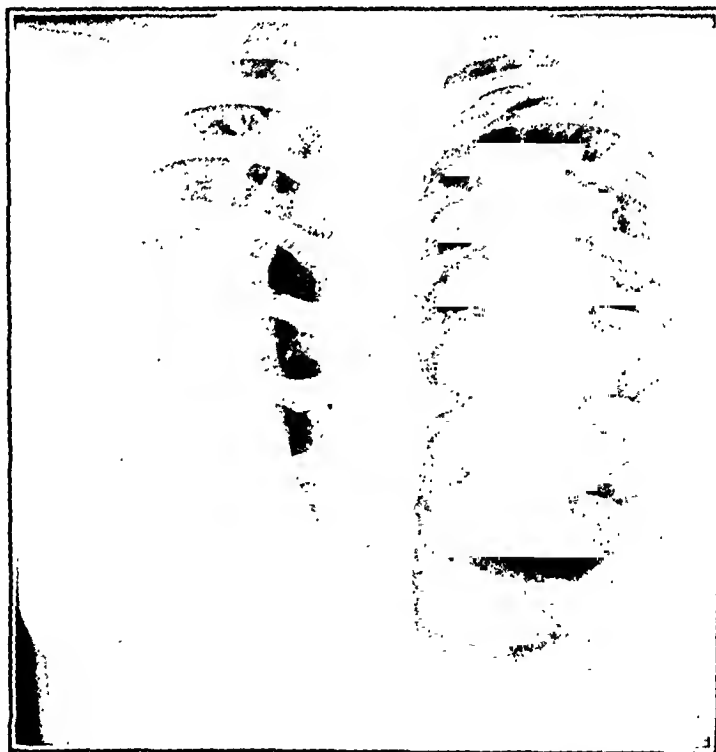


FIG. 2.—Postero-anterior chest roentgenogram made 4/18/36. The findings are very similar to those noted 8 years previously (Fig. 1). The cyst is perhaps a trifle larger at this time, as shown by the mediastinal displacement to the right. (Note: this film also was made by a previous consultant and not classified as showing any particular lesion.)

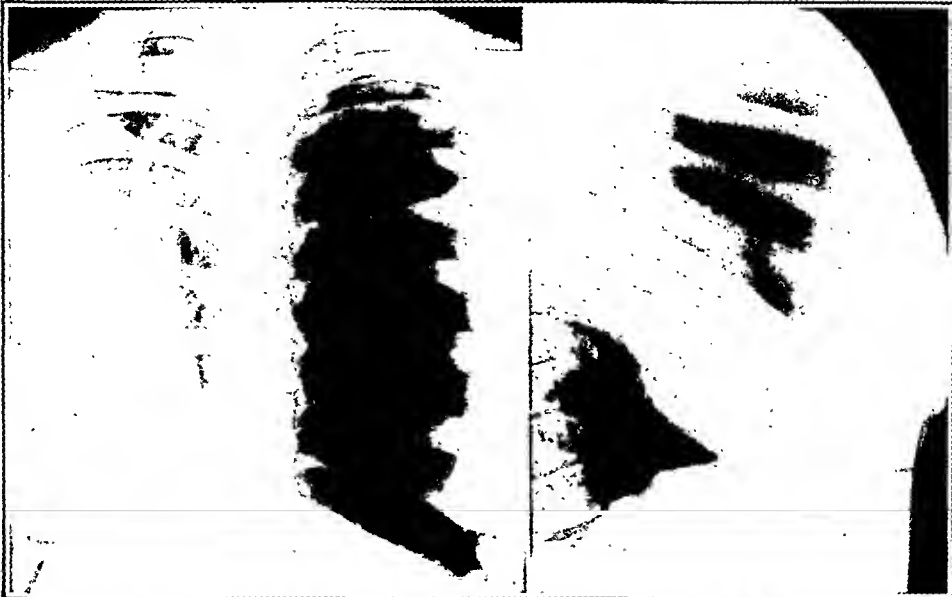


FIG. 3

FIG. 4

FIGS. 3 and 4.—Postero-anterior and left lateral roentgenograms made 5/26/37. The findings are similar to those noted 9 years previously (see Fig. 1). Massive left pulmonary pneumocyst or pneumocele. (Note: these films were made by the authors.)

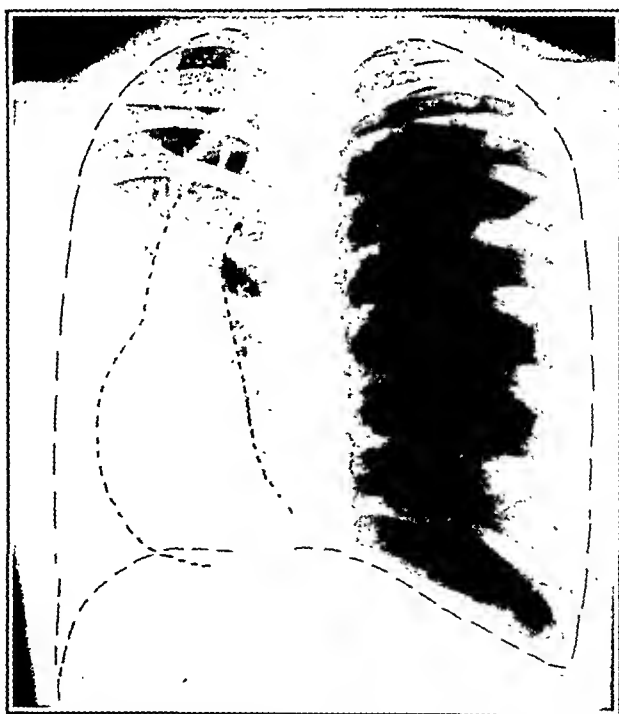


FIG. 5.—Postero-anterior roentgenogram made 5/26/37. Retouched to show position of heart and diaphragm more clearly. Massive left pulmonary pneumocyst.

seem handicapped physically in any way. Her mother states she is unusually alert and energetic and really seems stronger than her other two daughters.

The patient was examined again on January 27, 1938, 8½ months after her original examination. She had been perfectly well and working regularly. The physical examination was the same as previously; however, she was short of breath after hurrying to the office. The respiratory rate was then 26. She had gained 3 pounds in weight. The blood count showed 4,980,000 R.B.C., 106% hgb., and 12,900 W.B.C., with a normal distribution. Her vital capacity, done by Dr. J. K. Lewis, at Stanford University Hospital, was 1200 cc. of air, or only 27% of the expected normal.

Comment. Apparently the true nature of the pulmonary condition had not been previously recognized in our case, although the physical examination suggested the correct diagnosis to us before the Roentgen examination was made. The only case at all approaching this lesion in size that we have been able to find in the literature is one reported by Wood, in 1934, and subsequently by Kirklin,⁴ in 1936. In this case, the cyst also filled the entire side of one hemithorax and extended across the mediastinum into the upper portion of the opposite hemithorax.

In our case, the cyst presumably is connected with a bronchus which, being flattened by pressure of the cyst, has a ball-valve effect, permitting a little air to enter. The cyst therefore has some respiratory function. It is remarkable that the patient is able to get along so well with such a low vital capacity, and it is interesting to observe that the extreme degree of mediastinal hernia and dislocation which is present causes almost no symptoms.

Summary. The literature on cystic disorders of the lungs is briefly reviewed and a new classification of these lesions is suggested.

A case of enormous solitary cyst in an otherwise apparently healthy adult female is reported. It is not known whether the cyst in this case is congenital or acquired, but the history of infantile pertussis and pneumonia suggest that it is an acquired postinflammatory cyst of emphysematous origin.

Since completion of the above manuscript, there has appeared a report of a rather similar massive solitary pneumocyst in an infant five days old (Ford, F. A., *Radiology*, 30, 248, 1938). In that author's opinion, the cyst was congenital in origin; at autopsy, no macroscopic communication with the distended pneumocyst could be found. Microscopically, the wall of the cyst consisted of a surface layer of moderately high bronchial type epithelium supported on the connective tissue membrane

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SPONTANEOUS PNEUMOTHORAX.

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THE term pneumothorax was introduced by Itard in 1803, when he reported 5 cases which at autopsy revealed air in the pleural cavities. Laennec⁹ in 1819 was the first to diagnose pneumothorax in the living subject. In all of these cases the pneumothorax co-existed with far advanced tuberculous disease of the lungs with empyemata. In fact, both of these men were of the opinion that the air accumulation resulted from the decomposition of the pus and the absorption of the fluid. Houghton, in his "Encyclopedia of Medicine" published in 1834, disagreed with them and stated "it may be laid down as proved that where pneumothorax exists the air has been introduced from without."

Laennec, however, probably knew also of non-tuberculous pneumothorax, since in his book he discusses a case of rupture of air cells and pleura in a case of emphysema producing a pneumothorax. However he states "his notes of the case having been lost, he cannot make a positive assertion."

Following this, scattered reports began to appear in European literature on the subject. Thus in 1841 Saussier collected 147 hospital cases of spontaneous pneumothorax, in only 1 of which was there no apparent lesion of the lung. Biach in 1880 collected 918 hospital cases, 77% of which he states were of tuberculous origin. In 1884, West reported 101 cases from the London Hospital for Diseases of the Chest, 99 of which were definitely tuberculous. Morse¹¹ in 1900 reported a series of 51 cases of spontaneous pneumothorax from the Long Island Hospital in Boston occurring during the years 1882-1900. He found 70% of these tuberculous.

Ayer¹ in 1910 reported 72 cases occurring in the decade from 1900-1910 in the same hospital. He comments on the increased incidence over previous series and he ascribes it to better diagnosis because of the aid of the Roentgen ray. However, he states that in 23 cases air was found subsequent to chest tap. In these cases, the pneumothorax may well have been artificial.

These reports all emanated from hospitals for chronic pulmonary diseases; and it is not surprising that pneumothorax takes on a tuberculous significance. However, since the introduction of modern methods of treating tuberculosis, we recognize spontaneous pneumothorax as a fairly common complication of tuberculosis. It has been estimated by various writers that the incidence of spontaneous pneumothorax in tuberculosis is from 1 to 4%. It is found commonly in far advanced disease and implies a fatal prognosis as a rule.

The spontaneous pneumothorax seen in out-patient clinics and in private practice gives an entirely different conception from that outlined above, as was shown by Olbrechts¹² in 1930. He found 10 cases of spontaneous pneumothorax in 7000 hospital patients, only 2 of which were idiopathic. In 5000 out-patients he reports 17 cases, 13 of which were non-tuberculous. He also reports 2 cases from private practice which were of idiopathic origin. He tells us that in France spontaneous pneumothorax is called the pneumothorax of Conscripts because of its high incidence in healthy males of conscript age. The first report of spontaneous pneumothorax in the apparently healthy was published by Hall⁸ in 1887, based on 31 cases.

In 1902, Fussell and Riesman⁶ reported 2 cases and collected 56 others of non-tuberculous spontaneous pneumothorax. Emerson⁴ in 1903 surveyed 358 cases from the literature, reported 2 cases and observed that in 1 Osler ascribed the cause to rupture of an emphysematous bleb.

In 1934, Leggett, Myers, and Levene¹⁰ reported 31 cases from their clinic, 10 of which were patients of advanced tuberculosis, 6 of whom died within a short time. Two cases were secondary to bronchial asthma; 19 were of unknown etiology, 8 of whom had negative Mantoux tests.

Castex and Mazzei³ recently reported 3 cases of recurrent spontaneous pneumothorax in a group of 20 cases of spontaneous pneumothorax seen in private practice. They ascribe the accident to rupture of subpleural blebs during effort.

Kaergaard, the Swedish clinician, states that after long observation of a series of patients with systematic after-examination shows that in practice this disease has nothing to do with tuberculosis.

That spontaneous pneumothorax has been a problem for insurance companies is shown in a paper by Bartlett² who discussed the condition from the standpoint of the insurance examiner. He concludes, "that in spite of the presumptive evidence that these cases are usually tuberculous, it still remains a fact that the great majority of these cases get well and remain well and never develop tuberculosis. From the insurance point of view if the applicant is above average weight with a good family history and personal history and has been in good health since the attack, he may be safely accepted."

At the New Jersey Sanitarium for tuberculosis at Glen Gardner, New Jersey, 100 cases of supposedly minimal tuberculosis were admitted to the male service during the last 6 months of 1933. Among these were 4 cases of spontaneous pneumothorax in males who up until the accident had been healthy. The ages were 23, 29, 32, and 36. Two of the patients gave a family history of tuberculosis. One had blood-streaked sputum. The pneumothorax occurred on the right side in all 4 patients. These patients were put to bed and following expansion of the lung were subjected to

thorough study. Repeated sputa and Roentgen ray studies were negative. Sedimentation test was normal. After variable observation periods they were discharged. In a recent communication from Dr. S. B. English,⁵ the Superintendent, a follow-up on these patients indicates that none of them have developed tuberculosis. He also relates 5 other cases of spontaneous pneumothorax and 2 of recurrent pneumothorax who are non-tuberculous on study. He feels that the spontaneous pneumothorax seen in the healthy is an entirely different entity from those which complicate tuberculous diseases of the lung.

NEW JERSEY SANITARIUM CASES (ALL WHITE).

Patient.	Age (yrs.).	Side.	Admitted 1933.	Roentgen ray.	Repeated sputum.	Sedi- mentation test.
R.R.	23	R.	8/18	Neg.	Neg.	Neg.
V.C.	32	R.	7/15	"	"	"
J.A.	36	R.	7/7	"	"	"
R.R.	29	R.	10/27	"	"	"

At the Jefferson Hospital we have collected 20 cases of spontaneous pneumothorax in the interval from 1928 to the present time. All the cases were in males. The ages varied from 5 to 64 years. Ten of the cases occurring between 20 and 30 years of age. Ten cases were left sided; in 11, the accident was on the right. All gave a typical history of pain with dyspnea of sudden onset. The story as to what the patient was doing at the time of the accident is varied. It occurred during sleep, while eating, sitting, at rest, walking, shoveling, lifting heavy objects, and so on. All the patients were subjected to thorough study. Repeated sputa and Roentgen ray were negative, and in 6 cases bronchoscopic aspiration with study of the material aspirated.

Two patients had fluid—one a serous collection, one hemothorax. Both were negative after study of the fluid in addition to the above studies.

One patient died shortly after the accident and on autopsy bilateral far advanced tuberculosis was found.

Two patients were found to have pulmonary tuberculosis and were sent to sanatoria.

One patient was decompensated at the time of the accident. The accident simulated a coronary occlusion. He died a short time after admission. Postmortem revealed a ruptured emphysematous bleb; no evidence of tuberculosis.

The other patients showed reëxpansion of the lung in 3 to 4 weeks. All studies being negative, they were discharged. We have a definite follow-up only on 11 cases. These have remained well.

On 1 case in whom the accident occurred less than 2 years ago, there was a subsequent attack on the opposite side. He is being followed in the clinic and shows no evidence of tuberculosis (see F. P. below).

CASES FOLLOWED (ALL WHITES).

Patient.	Age (yrs.).	Side.	Admitted.	Roentgen ray.	Repeated sputum.	At present.
A.N.	21	L.	12/17/29	Neg.	Neg.	Working
S.Z.	41	R	10/29/31	"	"	"
J.R.	28	L	12/31/31	Pleural effusion	"	"
T.K.	22	R	10/11/32	Neg.*	"	"
J.C.	41	L	10/20/33	"	"	"
M.Z.	21	L	10/30/34	"	"	"
M.L.	64	L	4/27/35	"	"	"
O.H.	22	R	9/25/36	"	"	"
F.P.	17	R & L	12/ 7/36	"	"	"
			6/12/37			
J.D.	29	L	12/19/36	"	"	"
F.B.	21	R	10/25/37	"	"	"

* Negative on study, hemothorax negative on study and guinea pig negative.

CASES NOT FOLLOWED (ALL WHITES).

Patient.	Age (yrs.).	Side	Admitted.	Roentgen ray.	Repeated sputa.
P.S.	41	L	11/ 7/28	Neg.	Neg.
J.B.	52	R	.8/ 1/29	"	"
H.F.	50	R	5/19/31	"	"
H.L.	29	R	8/13/32	"	"
F.F.	5	L	6/17/34	"	"

The above 5 cases were also subjected to bronchoscopy; no cause for the pneumothorax could be found. Some material was aspirated which on study proved to be negative for the tubercle bacillus.

TUBERCULOUS CASES. POSITIVE SPUTUM (WHITES).

Patient.	Age (yrs.).	Side.	Admitted.	
V.W.	66	L	2/1/33	Bilat. pul. tbc. IIIc
J.B.	29	R	4/27/35	R. apical tbc. Ib

CASES THAT DIED (WHITES).

Patient.	Age (yrs.)	Side	Admitted.	
L.G.	42	R	3/25/30	Postmortem examination revealed bilateral far advanced pulmonary tuberculosis with right pneumothorax.
E.T.	47	L	1/25/32	Autopsy revealed myocardial failure with decompensation and a pneumothorax on the left side, the cause of which was found to be a ruptured emphysematous bleb.

Summary.—It is evident to the observer after a review of the literature and study of such cases that there are two types of spontaneous pneumothorax: symptomatic and asymptomatic. In the symptomatic group, we may place all the instances in which the accident complicated pulmonary disease and it is evident that it has been found in every type of lung lesion. Tuberculosis of course heads the list. It is in the asymptomatic group that we are at loss to explain the etiology. These are patients who have a negative family history of pulmonary disease, whose past medical history is negative, and who on physical examination following reexpansion of

the lung reveal no pathologic findings and whose Roentgen rays are normal. They return to their normal routine of life seemingly none the worse for the occurrence of pneumothorax. In some cases, Roentgen ray studies following reëxpansion have showed pulmonary cystic disease. In others, sub-pleural blebs have been found. In some instances chronic emphysema was blamed. But why should the accident occur in young people who rarely show emphysema and spare the aged in whom emphysema is fairly common? It is understandable also that an adhesion resulting from a healed tuberculous focus might present a weakened area where the accident can occur. We certainly cannot accept an infectious origin as the cause in these idiopathic cases since there is no pleural reaction. No adhesions form to prevent return attacks such as are seen following pulmonary infections and even after artificial pneumothorax. The condition certainly cannot occur in people with normal pulmonary and pleural tissue, for it is a known fact that a pressure from 100 to 300 mm. of water must be present in the alveoli to produce a rupture of the lung and pleura.

Schomer and Ehrlich¹³ in a recent paper discuss the condition and offer a possible explanation. They state that in normal respiration the gliding of visceral over parietal pleura causes a continuous shedding and regeneration of the pleural mesothelium. A slight defect in the regeneration at some point if located in a portion of the lung lobule or lobules involving one or more bronchioles, will, when accompanied by increased respiratory effort, cause a tear in the visceral pleura and produce pneumothorax. This sounds feasible but I think we might go even further and postulate a congenital pleural defect or an acquired pleural defect with a congenital anlage that in the normal course of events in the wear and tear of the human anatomy can rupture because of its inherent weakness. Such a weakened area in the pleura might even bulge due to tension and form a bleb. Some observers such as Ian Gordon⁷ of the Royal Chest Hospital in London insist that all cases are due to rupture of sub-pleural blebs or cysts. He described 5 cases in whom after reëxamination he could delineate these blebs or bullæ in the Roentgen ray plate. This we were unable to do.

Conclusions. 1. A review of the literature of tuberculous spontaneous pneumothorax and spontaneous pneumothorax in the apparently healthy has been given.

2. Twenty-four cases of spontaneous pneumothorax occurring in ambulant apparently healthy patients have been presented, 3 being tuberculous with well pronounced disease, 21 being non-tuberculous on study, 11 of whom have been followed from 1 to 9 years.

3. A theoretical explanation for the condition in the apparently healthy people has been discussed.

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A COMPARISON OF THE ETIOLOGY, DEATH RATES AND BACTEREMIC INCIDENCE IN THE MORE FREQUENT PRIMARY PNEUMONIAS OF INFANTS, CHILDREN AND ADULTS.*

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BECAUSE various organisms selectively attack the individuals of different age groups, it is important to present our experience with the age distribution, the blood invasiveness and the mortality for pneumonia due to the different organisms.

No explanation why the respiratory flora of infants, children and adults in the same community should be different has been offered. Under certain circumstances individuals who usually escape infection from certain pneumococci become vulnerable. In a number of instances, parents or grandparents have been infected by fondled infants or children, and infants have been infected from the nasal discharges of adults.

In his "Management of the Pneumonias," the senior author has discussed sex selection by certain pneumococci in adults.

We present a 7-year study of pneumonias (pneumococcic and non-pneumococcic) at Harlem Hospital contrasting in different age groups the etiologic agent, the fatality and the frequency in which the blood become invaded. We have classed as infants "children under 2 years of age," as children, "those from 2 years to puberty" and as adults, "all those beyond puberty." Only the 10 commonest of the 32 Cooper types are considered in this study of the pneumo-

* This study received financial support in part from the Metropolitan Life Insurance Company.

coccic pneumonias. The non-pneumococcic pneumonias are classified as "streptococcus," streptococcus beta, staphylococcus and *Bacillus friedländeri*.

Pneumococcic Pneumonias. The total number of pneumococcic pneumonias was: Infants (under 2 years), 381; children (2 to 12 years), 371; adults (12 years and over), 3065.

Distribution. The 10 most frequent pneumococci (types) given in Table 1 caused 63% of pneumonias among infants, 78.8% among children and 74.5% of the pneumonias among the adults.

TABLE 1.—INCIDENCE OF 10 MOST FREQUENT TYPES OF PNEUMOCOCCIC PNEUMONIAS.
July 1, 1928, to June 30, 1935.

Type.	Infants, under 2 years.			Children, 2 to 12 years.			Adults, 12 years and over.			Total, all ages.		
	Cases.	% of pneumococcic pneumonias (381).	S.E.	Cases.	% of pneumococcic pneumonias (371).	S.E.	Cases.	% of pneumococcic pneumonias (3065).	S.E.	Cases.	% of pneumococcic pneumonias (3817).	S.E.
I	20	5.3*	1.1	100	27.0*†	2.4	725	23.7*†	0.8	845	22.1	0.7
II	6	1.6*†	0.6	6	1.6*†	0.6	256	8.4*†	0.5	268	7.0	0.4
III	17	4.5*	1.1	18	4.9*	1.1	297	9.7*†	0.5	332	8.7	0.4
IV	16	4.2	1.0	22	5.9	1.2	179	5.8†	0.4	217	5.7	0.4
V	9	2.4*†	0.8	31	8.4	1.4	230	7.5	0.5	270	7.1	0.4
VI	54	14.2*†	1.8	26	7.0*	1.3	51	1.7*†	0.2	131	3.4	0.4
VII	6	1.6*†	0.6	12	3.2*	0.9	194	6.3*†	0.4	212	5.6	0.4
VIII	8	2.1*	0.7	11	3.0*	0.9	225	7.3*	0.5	244	6.4	0.4
XIV	77	20.2*†	2.1	54	14.6*†	1.8	87	2.8*†	0.3	218	5.7	0.4
XIX	27	7.1*	1.3	12	3.2	0.9	40	1.3*†	0.2	79	2.1	0.2
Total	240	63.0*	2.5	292	78.8*	2.1	2284	74.5	0.8	2816	73.8	0.7

* This rate is significantly different from total incidence for this type. That is, such a difference might have occurred not more than 5 times in 100 through chance errors of sampling. (Chi Square values were obtained by the formula given by Go† This rate is significantly different from the average.

† This rate is significantly different from the average.

S.E. = standard error.

continuity when
help of tables.)
group.

Among the infants, Pneumococci XIV, VI and I caused 39.7% of the pneumococcic pneumonias and among the children those types caused 48.6%. Among adults, Pneumococci I, III, II, V, VIII, VII and IV (in the order mentioned) account for most pneumonias.

Among adults and children, *Pneumococcus* I was present in approximately one-quarter of all cases and it was the most frequent type encountered. Among infants, it caused only about one-twentieth of the cases.

Pneumococci II, III, VII, and VIII were more frequent among adults than among infants or children; Pneumococci I and V occurred least frequently among infants. The occurrence of *Pneumococcus* IV was about the same for all groups. Pneumococci VI

and XIV were more frequent in infants than in children, and more frequent in children than in adults.

Fatality (Non-serum Cases). The pneumonias of adults were most fatal (26.9%). Those of infants were less fatal (16.2%) and those of children least fatal (4.1%) (Table 2).

TABLE 2.—MORTALITY OF 10 MOST FREQUENT TYPES OF PNEUMOCOCCIC PNEUMONIAS. NON-SERUM CASES.
July 1, 1928, to June 30, 1935.

Type.	Infants, under 2 years.				Children, 2 to 12 years.				Adults, 12 years and over.				Total, all ages.			
	Cases.	Deaths.	% mortality.	S.E.	Cases.	Deaths.	% mortality.	S.E.	Cases.	Deaths.	% mortality.	S.E.	Cases.	Deaths.	% mortality.	S.E.
I	12	1	8.3	8.0	43	1	2.3*†	2.7	82	23	28.0*	4.9	137	25	18.3	3.5
II	4	1	25.0	21.6	5	0	0.0*	..	116	52	44.8*	4.6	125	53	42.4*	4.4
III	12	2	16.7	10.8	16	1	6.3*	6.1	214	88	41.1*	3.4	242	91	37.6*	3.1
IV	13	3	23.0	11.5	18	0	0.0*	..	122	25	20.5*	3.7	153	28	18.3*	3.3
V	3	2	66.7†	26.3	20	0	0.0*†	..	147	27	18.4*	3.2	170	29	17.1*	2.9
VI	40	6	15.0	5.6	21	1	4.8*	5.3	38	7	18.4	6.3	99	14	14.1†	3.7
VII	4	1	25.0	21.6	11	0	0.0*†	..	144	26	18.1†	3.2	159	27	17.0*	2.9
VIII	8	2	25.0	15.4	10	0	0.0*†	..	163	22	13.5*	2.7	181	24	13.3*	2.5
XIV	56	9	16.1	4.9	41	4	9.8*†	4.6	72	23	31.9*	5.5	169	36	21.3	3.9
XIX	27	2	7.4*†	5.1	11	1	9.1†	8.7	31	10	32.3*	8.4	69	13	18.8	4.4
Total	179	29	16.2*	2.8	198	8	4.1*	1.4	1129	303	26.9*	1.3	1504	340	22.6	1.1

* Mortality rate for this type significantly different from the total.

† Mortality rate significantly different from the average for this age group.

S.E. = standard error.

Pneumonias due to Pneumococci I, XIV, and XIX among adults were more fatal than were the same pneumococcic pneumonias among infants or children. Pneumococcus IV had about the same mortality in adults as it had in infants (20.5% and 23% respectively), while the rate for children is significantly lower. Comparing the fatality of the 3 common pneumococci, Pneumococci I, VI and XIV among infants, children and adults, we found the following: Pneumonias due to Pneumococcus I and Pneumococcus XIV were most fatal in adults and least fatal in children. Pneumonias due to Pneumococcus VI had about the same death rate in both adults and infants (18.4% and 15% respectively) but it was more fatal in these groups than in children.

Frequency of Bacteremia (Non-serum Cases) (Table 3). While 23.5% of the pneumococcic pneumonias among adults had a positive blood culture, only 6.7% of the infants and 4.1% of the children showed blood invasion. Among the adults Pneumococcus II and III showed a significantly higher frequency of blood invasion than other types, 43.9% and 28% respectively. Although Pneumococcus XIV and XIX had had approximately the same frequency of blood invasion as Pneumococcus III, these percentages are not as

reliable, since they are based on a comparatively small number of cases.

TABLE 3.—INCIDENCE OF POSITIVE BLOOD CULTURE CASES IN THE 10 MOST FREQUENT TYPES OF PNEUMOCOCCIC PNEUMONIAS. NON-SERUM CASES.
July 1, 1928, to June 30, 1935.

Type.	Infants, under 2 years.				Children, 2 to 12 years.				Adults, 12 years and over.				Total, all ages.			
	Total cases.		Positive blood culture.		Total cases.		Positive blood culture.		Total cases.		Positive blood culture.		Total cases.		Positive blood culture.	
	No.	%.	S.E.		No.	%.	S.E.		No.	%.	S.E.		No.	%.	S.E.	
I	12	1	8.3	8.0	43	3	7.0	3.9	82	19	23.2	4.6	137	23	16.8	3.2
II	4	1	25.0	21.7	5	0	0.0	..	116	51	43.9†	4.6	125	52	41.6	4.4
III	12	0	0.0*	...	16	1	6.3	6.1	214	60	28.0†	3.1	242	61	25.2	2.8
IV	13	2	15.4	9.9	18	0	0.0	..	122	21	17.2	3.4	153	23	15.0	2.8
V	3	1	33.3	26.3	20	1	5.0	4.9	147	34	23.2	3.5	170	36	21.2	3.1
VI	40	2	5.0	3.4	21	0	0.0	..	38	5	13.1	5.5	99	7	7.1	2.6
VII	4	1	25.0	21.7	11	0	0.0	..	144	15	10.4†	2.5	159	16	10.1	2.4
VIII	8	1	12.5	11.7	10	0	0.0	..	163	31	19.0	3.1	181	32	17.7	2.8
XIV	56	3	5.4*	3.0	41	3	7.3	4.1	72	20	27.8*	5.3	169	26	15.4	2.8
XIX	27	0	0.0*	...	11	0	0.0	..	31	9	29.6*	8.2	69	9	13.0	4.0
Total	179	12	6.7	1.9	196	8	4.1	1.4	1129	265	23.5	1.3	1504	285	18.9	0.3

* Incidence for this type significantly different from total.

† Incidence significantly different from the average for this age group.

S.E. = standard error.

TABLE 4.—MORTALITY IN POSITIVE BLOOD CULTURE CASES IN THE 10 MOST FREQUENT TYPES OF PNEUMOCOCCIC PNEUMONIAS. NON-SERUM CASES.
July 1, 1928, to June 30, 1935.

Type.	Infants, under 2 years.			Children, 2 to 12 years.			Adults, 12 years and over.			Total, all ages.				
	Positive blood culture cases.	Positive blood culture deaths.	% mortality.	Positive blood culture cases.	Positive blood culture deaths.	% mortality.	Positive blood culture cases.	Positive blood culture deaths.	% mortality.	S.E.	Positive blood culture cases.	Positive blood culture deaths.	% mortality.	S.E.
I	1	1	100.0	3	0	0.0	19	15	79.0	9.3	23	16	69.6	9.8
II	1	1	100.0	0	51	39	76.5	5.9	52	40	76.9	5.7
III	0	1	1	100.0	60	58	96.7	2.3	61	59	96.7	2.3
IV	2	1	50.0	0	21	17	81.0	6.8	23	18	78.3	8.6
V	1	1	100.0	1	0	0.0	34	19	55.9	8.5	36	20	55.6	8.2
VI	2	2	100.0	0	5	3	60.0	21.8*	7	5	71.4	17.5
VII	1	1	100.0	0	15	10	66.7	12.2	16	11	68.8	11.5
VIII	1	1	100.0	0	31	13	42.0	8.8	32	14	43.8	8.8
XIV	3	2	66.7	3	1	33.3	20	15	75.0	9.7	26	18	69.2	9.0
XIX	0	0	9	7	77.8	13.8	9	7	77.8	13.5
Total	12	10	83.3	8	2	25.0	265	196	74.1	3.2	285	208	73.0	2.6

S.E. = standard error.

Fatality of Bacteremic Cases (Non-serum) (Table 4). The bacteremic death rate among the adults and infants was very high. Six of the 10 pneumococcic types had a mortality of 75 to 97% (Pneumococci I, II, III, IV, XIV and XIX) for adults. The average

mortality among adults was 74.1%, for infants 83.3% and for children 25%.

Non-pneumococcic Pneumonias. The total number of non-pneumococcic pneumonias was: Infants (under 2 years), 297; children (2 to 12 years), 285; adults (12 years and over), 508.

The cases grouped as streptococcus are those in which a hemolytic streptococcus (beta) was not found. They included cases from which was isolated streptococcus alpha, streptococcus gamma, or cases in which no classification of streptococci was attempted.

TABLE 5.—INCIDENCE OF 4 MOST FREQUENTLY OCCURRING CLASSIFICATIONS OF NON-PNEUMOCOCCIC PNEUMONIAS.

July 1, 1928, to June 30, 1935.

Organism.	Infants, under 2 years.			Children, 2 to 12 years.			Adults, 12 yrs. and over.			Total, all ages.		
	Cases.	% of non-pneumococcic pneumonias (297).	S.E.	Cases.	% of non-pneumococcic pneumonias (285).	S.E.	Cases.	% of non-pneumococcic pneumonias (508).	S.E.	Cases.	% of non-pneumococcic pneumonias (1090).	S.E.
Streptococcus	162	54.5†	2.8	193	67.8*†	2.8	251	49.4*†	2.2	606	55.6	1.5
Streptococcus beta	19	6.4*†	1.4	31	10.9†	1.8	76	15.0†	1.6	126	11.6	1.0
Staphylococcus	17	5.7†	1.4	16	5.6†	1.4	26	5.1†	2.5	59	5.4	0.7
Bacillus friedländeri . . .	0	0	36	7.1	1.9	36	3.3	0.6
Total	198	66.7*	2.8	240	84.3	2.1	389	76.6	1.1	827	75.9	1.4

* Incidence for this type significantly different from total.

† Incidence significantly different from the average for this age group.

S.E. = standard error.

Distribution. The four important classifications of non-pneumococcic pneumonias given in Table 5 represented 66.7% of all non-pneumococcic pneumonias in infants, 84.3% in children and 76.6% in adults. The incidence of streptococcus beta was less among infants, while staphylococcus occurred with approximately the same frequency in each group. There were no cases of *Bacillus friedländeri* among the infants or children but among the adults the incidence in the non-pneumococcic group was 7.1%

Fatality (Non-serum Cases). When invaded by staphylococci, children had a lower death rate than that of the total group (Table 6). In the cases grouped as streptococcus, adults and infants had a death rate which was about the same for each group (adults 18.3% and infants 19.8%). Children had a very low death rate in this group (1.6%). The infant death rate in the streptococcus beta cases is significantly lower than the total mortality in pneumonias caused by this organism. In adults, the mortality in *Bacillus friedländeri* cases was 82.1%.

TABLE 6.—MORTALITY IN 4 MOST FREQUENTLY OCCURRING CLASSIFICATIONS OF NON-PNEUMOCOCCIC PNEUMONIAS. NON-SERUM CASES.
July 1, 1928, to June 30, 1935.

Organism.	Infants, under 2 years.				Children, 2 to 12 years.				Adults, 12 years and over.				Total, all ages.			
	Cases.	Deaths.	% mortality.	S.E.	Cases.	Deaths.	% mortality.	S.E.	Cases.	Deaths.	% mortality.	S.E.	Cases.	Deaths.	% mortality.	S.E.
<i>Streptococcus</i> . . .	162	32	19.8*	3.1	193	3	1.6*	0.9	251	46	18.3*	2.4	606	81	13.4	1.4
<i>Streptococcus beta</i> . .	19	3	15.8*	8.3	28	6	21.4†	7.8	69	29	42.0†	5.9	116	38	32.8	4.4
<i>Staphylococcus</i> . . .	17	7	41.1	12.0	16	2	12.5*	8.3	24	13	54.2†	10.2	57	22	35.6	8.6
<i>Bacillus friedländeri</i> .	0	0	28	23	82.1	7.2	28	23	82.1	7.2
Total	198	42	21.2	2.9	237	11	4.6*	2.8	372	111	29.8*	2.4	807	164	20.3	1.4

* Mortality rate for this organism significantly different from total.

† Mortality rate significantly different from the average for this age group.

S.E. = standard error.

TABLE 7.—INCIDENCE OF POSITIVE BLOOD CULTURE CASES IN THE 4 MOST FREQUENTLY OCCURRING CLASSIFICATIONS OF NON-PNEUMOCOCCIC PNEUMONIAS. NON-SERUM CASES.
July 1, 1928, to June 30, 1935.

Organism.	Infants, under 2 years. Positive blood culture cases.				Children, 2 to 12 years. Positive blood culture cases.				Adults, 12 years and over. Positive blood culture cases.				Total, all ages. Positive blood culture cases.			
	Cases.	Deaths.	% mortality.	S.E.	Cases.	Deaths.	% mortality.	S.E.	Cases.	Deaths.	% mortality.	S.E.	Cases.	Deaths.	% mortality.	S.E.
<i>Streptococcus</i> . . .	162	0	0.0	..	193	0	0.0	..	251	9	3.6	1.3	606	9	1.5	0.5
<i>Streptococcus beta</i> . .	19	3	15.8	8.3	28	3	10.7	5.7	69	21	30.4	5.6	116	27	23.3	4.0
<i>Staphylococcus</i> . . .	17	5	29.4	11.0	16	1	6.3	6.0	24	13	54.2	10.2	57	19	33.3	6.4
<i>Bacillus friedländeri</i> .	0	0	28	17	60.7	9.2	28	17	60.7	9.2
Total	198	8	4.0	1.4	237	4	1.7	0.7	372	60	16.1	1.9	807	72	8.9	1.0

S.E. = standard error.

TABLE 8.—MORTALITY IN POSITIVE BLOOD CULTURE CASES IN THE 4 MOST FREQUENTLY OCCURRING CLASSIFICATIONS OF NON-PNEUMOCOCCIC PNEUMONIAS. NON-SERUM CASES.
July 1, 1928, to June 30, 1935.

Organism.	Infants, under 2 years.				Children, 2 to 12 years.				Adults, 12 years and over.				Total, all ages.			
	Cases.	Deaths.	% mortality.	S.E.	Cases.	Deaths.	% mortality.	S.E.	Cases.	Deaths.	% mortality.	S.E.	Cases.	Deaths.	% mortality.	S.E.
<i>Streptococcus</i> . . .	0	0	9	8	88.9	10.5	9	8	88.9	10.5
<i>Streptococcus beta</i> . .	3	3	100.0	..	3	2	66.7	..	21	19	90.5	6.4	27	24	88.9	6.0
<i>Staphylococcus</i> . . .	5	5	100.0	..	1	1	100.0	..	13	13	100.0	..	19	19	100.0	..
<i>Bacillus friedländeri</i> .	0	0	17	17	100.0	..	17	17	100.0	..
Total	8	8	100.0	..	4	3	75.0	..	60	57	95.0	3.3	72	68	94.4	2.8

S.E. = standard error.

Frequency of Bacteremia (Non-serum Cases) (Table 7). In these non-pneumococcic pneumonias the blood stream was invaded most frequently among adults 16.1%, infants 4% and children 1.7%. For staphylococci the percentages were: adults 54.2%, infants 29.4% and children 6.3%. For *Bacillus friedländeri* in adults the percentage was 60.7%.

Fatality of Bacteremic Cases (Non-serum) (Table 8). The death rate in patients with a staphylococcus, those grouped as streptococcus, streptococcus beta or *Bacillus friedländeri* positive blood culture was very high.

Summary. 1. Ten types of pneumococci represented 63% of all pneumococcic pneumonias in infants, 78.8% in children and 74.5% in adults. The mortality for these 10 types among adults was 26.9% among infants 16.2% and among children 4.1%.

2. In the pneumococcic pneumonias, the blood was most frequently invaded in adults (23.5%). The rate for infants was 6.7% and for children 4.1%. In the positive blood culture cases, infants showed the highest death rate (83.3%), adults 74.1% and children 25%.

3. The four important classifications of non-pneumococcic pneumonias represented 66.7% of all non-pneumococcic pneumonias in infants, 84.3% in children and 76.6% in adults. In these cases the death rate was 29.8% in adults, 21.2% in infants and 4.6% in children. These figures parallel those of the pneumococcic pneumonias.

4. In the non-pneumococcic pneumonias, the blood was most frequently invaded in adults (16.1%). In infants it was 4% and for children 1.7%. In the positive blood culture cases, infants showed the highest death rate (100%), adults 95% and children, 75%.

Assistance in the statistical analysis was rendered by Evelyn Greenbaum and Mildred Swearngin.

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BENZEDRINE SULPHATE IN PERSISTENT HICCOUGH.

A REPORT OF 2 CASES.

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PERSISTENT hiccough, irrespective of its etiology, has been variously treated with sedatives, antispasmodics, nasal cocaine-epinephrine packs, carbon dioxide inhalation, lavages, ingestion of fluids,

and surgery. Relief is problematic and usually not the direct result of standard remedies. Having a postoperative patient who did not respond to any of the usual remedies and who had hiccupped to the point of an alarming exhaustion, I decided to try benzedrine sulphate (benzyl methyl carbinamine sulphate or beta-phenylisopropylamine sulphate)—a drug which from previous reports in the literature seemed to have a specific action in relaxing smooth muscle of the gastro-intestinal tract.

Case Histories.—**CASE 1.** A male patient, aged 56, had recently been under treatment for duodenal ulcer from which he had completely recovered. Soon after that he had a fall and sustained a fracture of the ligamentum patellæ, which was sutured under ether anesthesia.

About 12 hours after the operation he began to hiccup continuously. Oral administration of various gastric and general sedatives proved ineffective; inhalations of carbon dioxide brought relief for only short intervals of 30 to 40 minutes. This continued for over 48 hours when the patient began to show signs of exhaustion. The following night his condition became rather alarming. Within the space of 8 hours he received 6 grains of sodium amytal without benefit, and 2 hypodermic injections of morphine of $\frac{1}{4}$ and $\frac{1}{2}$ grain, respectively, which induced sleep for only half an hour. Various physical measures such as change of position, abdominal compression, pressure on the phrenic nerve and so on, proved entirely useless.

I decided to try benzedrine sulphate in spite of the risk of keeping the patient awake when he needed sleep so badly. After a dose of 20 mg. there was a spectacular cessation of the hiccup and the patient went to sleep for several hours. The drug was repeated twice that day in 10 mg. doses. The hiccup diminished very markedly and ceased altogether the following day.

CASE 2.—A male patient, aged 65, has had annually recurring gastro-intestinal attacks since an appendectomy 30 years ago, although Roentgen ray reveals no organic lesions. These attacks include a loud, crowing hiccup at the rate of 3 to 4 a minute, which does not yield to lavages or other therapeutic measures until the underlying condition has been remedied. The treatment for achylia gastrica and neurotic symptoms with hydrochloric acid, lavages and sedatives is usually successful within 2 weeks.

When he came to me on February 25, he had the usual symptoms, with the addition of diarrhea, and including a hiccup which had been troubling him for several days. The hiccup was arrested in 15 minutes after administration of 10 mg. of benzedrine sulphate. I prescribed 1 or 2 tablets to be taken in the morning and 1 at noon if necessary. This medication never failed to control the hiccupping within 15 to 20 minutes. The other symptoms responded to treatment within a week, when all therapy was discontinued.

Comment. The literature indicates that the effectiveness of benzedrine sulphate in these 2 cases may be explained by its specific antispasmodic action. Prominent among the numerous uses to which it has been put is the relaxation of smooth muscle of the gastro-intestinal tract. Myerson and Ritvo⁴ suggested benzedrine sulphate as an aid to gastro-intestinal visualization in roentgenology. They recommended an average oral dose of 30 mg. for relieving spasm of the gastro-intestinal tract. Ritvo⁵ has since elaborated

this study and confirmed the original findings. Beyer and Meek¹ reported that 30 mg. of benzedrine sulphate administered to dogs increased gastric tone and emptying time for 8 minutes, but with marked diminution in 40 minutes. Smith and Chamberlin,⁷ administering 20 mg. to humans, found an increase in stomach emptying time, decrease in peristalsis and relaxation of the spastic duodenum and colon. Van Liere and Sleeth⁸ repeated Beyer and Meek's experiment, confirming their conclusion as to the delay in gastric emptying time, but denying an original increase in rate. Finally, it has been found that benzedrine sulphate relaxes the gall bladder and increases its emptying time.^{2,3,6}

The two cases are presented as a suggestion to other investigators for further study of the use of benzedrine sulphate in persistent hiccough. Since much remains to be learned about the etiology of the condition, it would be interesting to study the effect of benzedrine sulphate in various types. It is not suggested that it would always be of benefit in cases where the hiccough seems to be of neurotic or emotional origin. While in certain instances the euphoric effect often observed might prove to be a contributory factor in controlling neurotic manifestations, yet on the other hand nervous patients sometimes have symptoms which are aggravated by benzedrine sulphate.

In postoperative hiccough, or in cases where the hiccough appears to be of gastro-intestinal origin, the first principle of therapy should be to improve the underlying condition. In the meantime, the relief afforded by benzedrine sulphate may in many cases shorten the time of recovery, as is illustrated by Case 2. In both cases it is apparent that benzedrine sulphate, perhaps through its action on smooth muscle, controlled the spastic condition responsible for the hiccough.

Summary. Benzedrine sulphate was found to be of value in relieving 2 cases of persistent hiccough. The explanation seems to lie in its specific action of relaxation of smooth muscle.

Since the above was submitted I had another patient, a man of 21 years, who had been hiccoughing for more than 24 hours. Another physician had prescribed some medication which failed to stop the hiccough. The physical examination and the history yielded no clue as to the cause of the hiccough. The administration of 1 tablet of benzedrine sulphate stopped it in about 45 minutes.

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STANDARDS FOR MAXIMUM RETICULOCYTE PERCENTAGE AFTER INTRAMUSCULAR LIVER THERAPY IN PERNICIOUS ANEMIA.

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COMPARABLE to the standards for reticulocyte response after oral liver therapy of pernicious anemia compiled by Riddle² and for desiccated stomach and intravenous liver therapy compiled by Bethell and Goldhamer,¹ a set has been developed for intramuscular treatment.

The present series consisted of 128 patients with pernicious anemia treated with liver extract intramuscularly. From this group, 22 patients treated at this institute, and 31 patients treated by others elsewhere were selected as most complete for this study. These patients showed true pernicious anemia in relapse, and had not had specific therapy for 2 months or longer periods before the treatment was started. The liver extracts were of different types and the patients were selected because the therapy, in the doses given, caused an adequate and progressive increase in the number of red blood cells. Dosage varied from 1 to 7 injections per week, which was the average time required for the attainment of the maximum reticulocyte response. The material given represented liver extract made from 100 to 400 gm. of liver, although in actual units it probably did not represent more than an average of 1 or 2 units per day; in most cases, 1 unit.

The maximum reticulocyte percentage responses were plotted against the initial red blood cell count. Averages were then calculated for red blood cell counts of 0.5 to 1 million; 1.1 to 1.5 million; 1.6 to 2 million, and so on. The curve of the averages, when plotted, gave a line, any point of which could be calculated from the formula

$$R = \frac{82 - 22 E_0}{1 + 0.5 E_0}$$

in which R equaled the maximum reticulocyte per cent reached during the course of the reticulocyte response and E_0 the red blood cell count on the day that therapy was started.

The following table gives the maximum reticulocyte percentages calculated for different initial red blood cell counts.

TABLE 1.—MAXIMUM RETICULOCYTE PERCENTAGE, CORRELATED WITH THE INITIAL RED BLOOD CELL COUNT (E_0) AFTER INTRAMUSCULAR LIVER EXTRACT IN PERNICIOUS ANEMIA (ISAACS AND FRIEDMAN).

$R = \frac{82 - 22 E_0}{1 + 0.5 E_0}$			
E_0 .	Retic. %.	E_0 .	Retic. %.
0.4	61.0	2.0	19.0
0.5	56.8	2.1	17.5
0.6	52.9	2.2	16.0
0.7	49.3	2.3	14.6
0.8	46.0	2.4	13.3
0.9	42.9	2.5	12.0
1.0	40.0	2.6	10.8
1.1	37.3	2.7	9.6
1.2	34.8	2.8	8.5
1.3	32.4	2.9	7.4
1.4	30.1	3.0	6.4
1.5	28.0	3.1	5.4
1.6	26.0	3.2	4.5
1.7	24.1	3.3	3.5
1.8	22.3	3.4	2.7
1.9	20.6	3.5	1.8

Summary and Conclusion. After intramuscular liver therapy in pernicious anemia, a definite relation exists between the maximum reticulocyte percentage (R) reached during the period of the reticulocyte response and the initial red blood cell count (E_0). This relationship is expressed by the formula

$$R = \frac{82 - 22 E_0}{1 + 0.5 E_0}$$

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BOOK REVIEWS AND NOTICES

FUNCTIONAL ACTIVITIES OF PANCREAS AND LIVER. A Study of Objective Methods for the Estimation of Function Levels in Health or Disease. By CHARLES W. McCLURE, M.D., Gastroenterologist to Fifth Medical Service, Boston City Hospital; Assistant Professor of Gastroenterology, Boston University School of Medicine. Special Chapters by TAGE CHRISTIANSEN, M.D., Resident Physician, Medical Department, County Hospital of Copenhagen, Denmark; and the late ALLAN W. ROWE, PH.D., formerly Director of Research, Evans Memorial, Boston, Mass. With a Foreword by SAMUEL WEISS, M.D., F.A.C.P., New York. Pp. 318; 66 illustrations. New York: Medical Authors' Publishing Company, 1937.

THIS monograph mostly contains previously published original data on studies of pancreatic and hepatic secretions. A final section is devoted to methods and technical procedures used in the studies. The detailed presentation of the material is such that the underlying purposes of the investigations are often unclear, and the results difficult of interpretation. The lack of critical analysis of the data presented in such profusion robs the volume of interest except to those intimately connected with this particular branch of research. K. E.

DISEASES OF THE BLOOD. By CYRUS C. STURGIS, M.D., B.S., Professor of Medicine, University of Michigan Medical School; Director, Thomas Henry Simpson Memorial Institute for Medical Research, and RAPHAEL ISAACS, A.B., A.M., M.D., Associate Professor of Medicine, University of Michigan Medical School; Assistant Director, Thomas Henry Simpson Memorial Institute for Medical Research. Edited by MORRIS FISHBEIN, M.D. Pp. 302; 2 figures. New York: National Medical Book Company, Inc., 1937.

DESIGNED, according to the Preface, for the use of the General Practitioner, this booklet is chiefly concerned with diagnosis and treatment. For "details of technique" the reader is referred to "special books on this subject." Even for the General Practitioner, however, diseases of the blood cannot be presented adequately in a work of this size—one, too, that is even smaller than the size of the book indicates, on account of the large print and wide spacing used.

The authors, both well known for their good work in hematology, apparently have not been stimulated by their task, as the presentation is distinctly not up to their usual standard. Though actual errors are infrequent, the careful discrimination that is so essential in condensations of this sort is frequently missed. The articles listed at the end of each section, an item emphasized in the Preface, are but few, in some cases missing entirely, and not always well chosen. Altogether, with the excellent books of various sizes and costs that already exist in this field, this latest cannot be recommended as the best available for the many physicians who feel the need of a small book on the subject. E. K.

BARON CONSTANTIN VON ECONOMO. His Life and Work. By his wife and by PROF. J. VON WAGNER-JAUREGG. Translated from the second German edition by RAMSAY SPILLMAN, M.D. Pp. 126; illustrated. Burlington, Vt.: Free Press Interstate Printing Corporation, 1937. Price, \$2.00.

"VON ECONOMO's death from coronary occlusion in 1931 at the age of 55 removed at the height of his career a figure unique in scientific history. He was known as the world's foremost investigator of cerebral histology; he was the discoverer of encephalitis lethargica; and he was a pioneer aviator, flying his own plane as early as 1908. The translator, who is not a neurologist but a Roentgenologist, regarded this biography as so great a human document that he underwrote its publication in English in the hope that it would fall into the hands of students of medicine. . . . The English text is augmented by the three papers which von Economo read in New York in 1929; these have hitherto been available only in the files of special journals." The volume concludes with a bibliography of 69 scientific publications.

E. K.

LECTURES ON THE EPIDEMIOLOGY AND CONTROL OF SYPHILIS, TUBERCULOSIS, AND WHOOPING COUGH, AND OTHER ASPECTS OF INFECTIOUS DISEASE (The Abraham Flexner Lectures, Series No. 5). By THORVALD MADSEN, M.D., Director of the State Serum Institute of Denmark, Copenhagen; Chairman of the Health Committee of the League of Nations. Pp. 216; 21 illustrations. Baltimore: The Williams & Wilkins Company, 1937, for Vanderbilt University. Price, \$3.00.

THIS little book, giving Abraham Flexner lectures by an internationally known and distinguished hygienist, the Director of the State Serum Institute of Denmark, appears under a title which by no means does justice to its extremely interesting content. The lecture on the control of syphilis is, of course, of interest to public health officers in the light of the present campaign, but contains no essential material not now familiar through the report of the New York Commission, to practically all interested American physicians. It lays the well-known emphasis upon the Scandinavian program and the special conditions of Scandinavian life, of population characteristics and reactions to legislative and public health control, which are deemed largely responsible for the program's success. Among the most interesting and suggestive chapters are those which summarize the present-day knowledge of the mechanism of bacterial infection and the influence of seasons on infection. The bibliography attached to each of these chapters contains the necessary documentation and suggested reading for all who would be broadly informed on these growingly important medical problems. The chapter on whooping cough emphasizes the morbidity and mortality of a disease too often lightly considered. Madsen regards the etiology of whooping cough as established in the Bordet-Gengou bacillus, as against the filterable virus concept. He describes in discussion the question of the efficiency of vaccination, the controlled experiment conducted in the Faroe Islands. From this study, he concludes that the preventive value of the Bordet-Gengou vaccine is practically zero, but that the mortality in the non-vaccinated group is 12 times that of the vaccinated, and that the course of the disease is much less severe in vaccinated individuals.

When one considers its relatively low price, this book should find a place in the library of practically every physician broadly interested in medicine as well as specially interested in public health.

J. S.

A BIBLIOGRAPHY OF THE WORKS OF AMBROISE PARÉ: Premier Chirurgien & Conseiller du Roy. By JANET DOE, Assistant Librarian of the New York Academy of Medicine. Pp. 265; 30 illustrations. Chicago: The University of Chicago Press, 1937. Price, \$5.00.

ONE of the most interesting figures in medical history and one of the greatest of pre-Listerian surgeons, Paré has long commanded the attention of medical historical writers. Only once before, however, and that by Malgaigne almost a century ago, has a bibliography of his works been published. The present volume, therefore, prepared by one long familiar with medical libraries, is obviously valuable if only for its dry bibliographical details. Much more valuable is it, however, because Miss Doe has profited by her four-year study of the man as well as his works to build up in introductory and interlarded remarks a delightful picture of a vain, impetuous and ambitious, yet lovable, simple and kindly character. If her scholarship needed demonstration, this could be found in her description of six unique editions "previously unknown to bibliographers." Following the method of Keynes' bibliography of Harvey, some owners of various editions have been indicated by initials. Thus 21 copies of the first edition (1575) of the Collected Works (in French) are listed; but already another copy has been reported from the Duke Hospital Library. E. K.

LEUKEMIA AND ALLIED DISORDERS. By CLAUDE E. FORENER, A.M., M.D., Assistant Professor of Clinical Medicine, Cornell University Medical School, and Assistant Attending Physician, New York Hospital, etc. Pp. 333; 73 illustrations and 6 colored plates. New York: The Macmillan Company, 1938. Price, \$5.00.

THE author has collected a great deal of information in this compact yet exhaustive monograph. The data have been scanned in the particular light of newer pathologic physiology and morbid anatomy, as stated in the Preface. A large section has been devoted to treatment. The charts, clinical and microscopic photographs, as well as the color plates, are good. Typographical errors are few. The bibliography, covering 65 pages, is excellent.

Though, on the whole, the facts have been well presented, the Reviewer is left with the feeling that the confusion at present existing in this field of blood diseases has been in no way lessened. The inclusion in one discussion of a large number of disease entities, all presumably "allied" to the leukemias, but owing their alliance on meager proof, is open to some question.

The reader will fail to find many definite statements concerning the opinions of the author. More numerous paragraphs in résumé of the work by other investigators in the field herein quoted might have made the book more readable.

This monograph will be found to be of great assistance to those working in this narrow field, particularly if a comprehensive one-volume summary is desired. A. S., JR.

PLAY AND MENTAL HEALTH. Principles and Practice for Teachers. By JOHN EISELE DAVIS, M.A., Veterans' Administration Facility, Perry Point, Md. Pp. 202. New York: A. S. Barnes & Co., 1938. Price, \$2.50.

THIS authority on recreational therapy writes with great clarity on the philosophy of play as conducive to a wholesome mental expression, and finally as leading to socialized behavior. Parts of the chapters are as

follows: Chapter I. Play and Psychic Adjustment. Coöperation and competitive experience, fanciful and real living, the timid child, and play of the mentally well and the mentally ill. Chapter II. Play and Adjustment to the Outside World. Play and the child's language, boys and girls at play, play and work, play and intelligence, and growing into reality; an unusually instructive part is, "Be Your Age;" here is discussed the relationship of play activities to the chronologic age: "The six-year-old enjoys dramatic play and is interested mostly in toys utilized in physical activity." "The eight-year-old has become self-assertive and is interested in games involving individual competition." "The twelve-year-old has reached the 'gang age.'" "The fourteen-year-old grouping is not homogeneous in its interest." "The sixteen-year-old has reached the stage of definite interest in the opposite sex, he likes athletics of the more mature form, his individuality causes conflicts between him and his parents and his teachers." Chapter III. Play and Behavior. Building the structure of conduct, moralizing about play, play and character formation, and education for personality. Chapter IV. Happy Socialization. Cramping natural play, the psycho-analytic approach of play ways to education, natural discipline through play, and play and culture. A good bibliography including relevant articles is found at the end of each chapter, and there is an informative index. This unusual book merits a wide circulation. N. Y.

DIE WERKE DES HIPPOKRATES. Die Hippokratische Schriftensammlung in neuer deutscher Uebersetzung. Herausgegeben von DR. MED. RICHARD KAPFERER, Bad Wörishofen und München, unter Mitwirkung von PROF. DR. GEORG STIDER, Würzburg, u. a. *Teil 8: Die Drüsen/Die Stellen am Menschen/Die Flüssigkeiten und Ihre Anwendung* (On the Glands; Of the Places in Man; On the Use of Fluids) (Pp. 108. Price, Rm. 8.50, 1936). *Teil 13: Vorhersagungen, I. Buch/Koische Vorhersagungen* (Prorrhetics, 1 Book; Coan Praenotions) (Pp. 106. Rm. 8.00, 1936). *Teil 15: Die Anatomie/Die Natur der Knochen/Das Fleisch der Vorhersagungen 2. Buch* (On Anatomy; On the Nature of the Bones; On Fleashes; Prorrhetics, 2 Book) (Pp. 96. Price, Rm. 5.50, n.d.). *Teil 18: Die Krankheiten 2. Buch/Die Krankheiten 3. Buch* (Of Diseases, Books 2 and 3) (Pp. 115. Price, Rm. 6.50, n.d.). Stuttgart: Hippokrates Verlag G. m. b. H. (To be published in 25 parts costing ca. Rm. 100; card binding.)

PART 8. The short book on the "Glands," occupying but 10 pages in this translation, contains several important medical concepts that have a surprisingly modern ring. The glands, mostly lymph nodes, are known to be widely scattered over the body and to swell in many fevers. They are regarded as filters of harmful material, which they transform, and also as mechanisms to prevent an excess of fluid in the body. Tonsils and brain are both included among the glands, and it is recognized that all of them can do either good or harm to the body. Seven "flows" are recognized, from the ears, eyes, nose, tonsils, stomach, spinal canal and hip joint. The text followed is that of Littré. The style lacks the clarity of the authentic Hippocratic books.

From "The Places in Man" comes the still persisting doctrine that constipation produces autointoxication of distant muscles and joints. The seven "flows" from the head cavity are here differently described than in "Glands" and others added. The catarrhs in various parts of the body are established, and rheumatism (hence the name!) is included in this category. This book is included in Erotian's list of true Hippocratic works. The text followed in this translation is that of Littré.

"On the Use of Fluids" not only outlines the uses of hot and cold water in non-feverish conditions—their use in fevers being given in "Diet in Acute Diseases"—but also of salt water, vinegar and wines. Erotian classed the book as authentically Hippocratic. The text followed here is that of the *Corpus medicum Graecorum*.

PART 13. The importance placed on prognosis and the ability to foretell correctly the course of the patient's illness is one of the most characteristic features of the Hippocratic School. Four books of the *Corpus* deal with this subject: in addition to Hippocrates' own book on Prognosis and the two on Prorrhethics and the *Coan Praenotions*. The authorship of the last three has continued to be a subject of controversy since Galen and Erotian rejected the second Prorrhethics (*Part 15*). The first Prorrhethics represents the effort of an acute observer, confronted by a mixed lot of fevers, to give a basis for correct answers about the chances of life and death, and when and in what guise the crisis will appear. The *Coan Praenotions*, which repeats most of the statements of the Prorrhethics, goes much further; in fact is practically an attempt at a general textbook on Prognosis in the broad Hippocratic sense. It is opposed to the famous "Cnidian Sentences."

In the 15th pamphlet have been collected the three brief treatises that deal with the structure of the body. The shortest of these, "On Anatomy," is a fragment consisting of 15 terse paragraphs, each giving a very brief description of an important organ. "On the Formation of the Bones" has only 2 paragraphs on bones; much more space being given to Polybus, because Aristotle quotes Section 9 of this pamphlet word for word as coming from that writer. The preceding section, however, has been just as circumstantially ascribed to a certain Syennesis. "On the Soft Parts" is a fanciful and fantastic explanation of the formation of various parts of the body on the basis of different mixtures of the 4 humors. It contains one strikingly modern statement, however, to the effect that shed blood will not coagulate after being whipped. The second book of "Prognostics," though not recognized by Galen and other Classical writers as part of the *Corpus Hippocraticum*, has been included in this edition, as being characteristic of the teaching of the School of Cos.

PART 18. These two books logically follows those of Part 8 in that they are built on the theory of the seven "flows" from the cranial cavity. As a commentary on Hippocrates' own work, "Diet in Acute Diseases," they offer a good view of the Greek concept of the relations between the head and the body and the treatment of various head conditions. In the third book are given many details of how to rid the body of the impurities of disease by bleeding, sweating, purging, vomiting, sneezing. Diet and various hydrotherapeutic measures are also considered. Many will be surprised to read in Book 3, Chapter 10, a recommendation for intubation in angina, rediscovered in 1790; and in Book 2, Chapter 61, the use of direct auscultation in pulmonary edema, thereafter lost for 2200 years. The authorship of this book is obscure; Galen thought it to be Cnidian; Dioscorides, that it was written by Hippocrates the younger; while Littré found such a close resemblance to "Diet in Acute Diseases" that he regarded it as at least very close to the true Hippocratic school and period. Littré's text is followed in this translation.

E. K.

THE LIFE OF CHEVALIER JACKSON. An Autobiography. Pp. 229; 80 illustrations, many in full color. New York: The Macmillan Company, 1938. Price, \$3.50.

SELDOM, indeed, under the conditions of modern medicine is it given to one man to create a new specialty, carry it to an advanced stage of per-

fection so that countless lives are saved and suffering relieved thereby, and also so to train assistants and students that the continuation of the work is assured. Intubation, to be sure, had been introduced by Horace Green and O'Dwyer and the beginnings of esophagoscopy started by Morell Mackenzie, just as the way to most great medical advances has been indicated by earlier work. But the foundation and establishment of endoscopy (bronchoscopy, esophagoscopy) is just as much due to the author of this book as bacteriology is to Pasteur and Koch, combined. Who, then, would not be eager to read this first-hand account, to be charmed all the more by the simple, naive and interesting way in which the many-sided story is told?

Chevalier Jackson is an artist as well as a scientist—how much his science owes to his art would be hard to say—and his art is amply manifest here in his choice of topics and charming style. Fortunate are those who have heard and seen his bimanual "chalk talks" in medical halls, who have been attracted by his wood-turning or etching or received charming Christmas cards of outdoor sketches in oil.

Remarkable, also, are the details of Chevalier Jackson's picturesque life. Sensitive always to all forms of suffering, he passed his boyhood amidst an unusual amount of cruelty to children and animals, scenes that had their counterpart in the suffering from disease that he later encountered. To combat this appears to have been a compelling motive in his life work, even to the point of requiring of him experimentation on the living animals he loved. Financial and health difficulties were overcome without complaint and even made to contribute to an unusually successful career. In this career life indeed began at 40, as the appended *Curriculum Vitæ* shows; fortunately it still continues at 73. Childlike in his simplicity, and with a complete absence of boasting, he writes such phrases about his work as "This was a great achievement," as naturally and unconcernedly as "I felt that it was all my fault." It may be as true today as in the beginning of our era that a child shall lead them.

Colored plates frequently interspersed through the text are supplemented by 60 or more full-page black and whites (following the Index) that add not a little to the author's life picture. We hope that our view will be confirmed that this will stand as a great, as well as a charming, medical autobiography.

E. K.

A BIOLOGICAL APPROACH TO THE PROBLEM OF ABNORMAL BEHAVIOR. By MILTON HARRINGTON, M.D., Psychiatrist, Institution for Male Defective Delinquents, Napanoch, N. Y.; formerly Consultant in Mental Hygiene, Dartmouth College. Pp. 459; illustrated. Lancaster, Pa.: The Science Press Printing Company for the author, 1938.

THIS book, a sequel to *Wish Hunting in the Unconscious*, presents a bio-mechanistic theory of the psychology of normal and abnormal behavior. It is assumed that a scientific theory is valid if it is useful in giving order and meaning to things which lacked order and meaning before. The shortcomings of other schools of psychopathology, especially the animistic, are pointed out.

Behavior consists of stimulus and response. The nature of the organism is implied as a factor determining the response. The cerebral apparatus is only an adjunct to the stimulus—response mechanism. A stimulus gives rise to tension in the nervous system, necessitating some sort of action. If the right sort of action ensues, the tension is relieved, satisfaction is attained and the organism is in a state of mental adjustment. Behavior is normal if it is fit for the situation in which it occurs. Bodily ailments are considered to be more important than psychologic factors in the production of mental ills.

Unsatisfactory forms of behavior are due to unfitness of the organism for its environment. The environment may be unfavorable or the organism may have defects and limitations. If the behavior does not bring about a relief of tension, the organism is in a state of non-adjustment. This may lead to a neurosis or a psychosis. If relief of tension is brought about in the wrong way, the organism is in a state of maladjustment. This behavior is usually called crime or sin. This behavior is regrettable that a mechanistic theory should not utilize present-day knowledge of the anatomy and physiology of the nervous system. Contrary to the author's statement, specific sense organs or nerve terminals for pain, as well as pain fibers, have been demonstrated. This book should prove interesting to the neurologist or psychiatrist who wishes to be well-read. The seeker for a theory to displace other schools of psychopathology is very likely to be disappointed. L. S.

MEMORANDUM BOOK OF A TENTH-CENTURY OCULIST for the Use of Modern Ophthalmologists. A Translation of the Tadhkirat of Ali ibn Isa of Baghdad (cir. 940-1010 A.D.), the most complete, practical and original of all the early textbooks on the Eye and its Diseases. The First Edition in English by CASEY A. WOOD. Pp. 260; 21 illustrations. Chicago: Northwestern University, 1936. Price, \$8.00.

The author, one of our leading ophthalmic historians, several years ago published an English translation (Stanford University Press, 1929) of Beneventus Grassus' *De Oculis* (1474), the first printed work on ophthalmology. He now again contributes to medical history, with this far more difficult translation from the Arabic, of "what is generally regarded as the most original and complete of all the early written treatises on the same subject." Of its three books—on Anatomy and Physiology, External Diseases of the Eye and Internal Diseases of the Eye—that on external diseases is much the longest. This, too, contains the interesting chapters on cataract and operations for its relief. In addition to the translation itself, Dr. Wood has included an all-too-brief chapter of Comments and Commentaries on the Memorandum Book and another on Five Centuries of Arabic Authors and their Treatises on the Eye. Though a Bibliography is appended, an Index is unfortunately lacking. Beautifully prepared by the Lakeside Press for Northwestern University, this book should be welcomed as a credit to American scholarship and as a valuable possession by ophthalmologists and medical historians. E. K.

CLINICAL ROENTGEN THERAPY. Edited by ERNST A. POHLE, M.D., Ph.D., F.A.C.R., Professor of Radiology; Chairman, Department of Radiology and Physical Therapy, University of Wisconsin, Madison, Wis. Foreword by GEORGE W. HOLMES, M.D., Roentgenologist to the Massachusetts General Hospital and Clinical Professor of Roentgenology in Harvard Medical School, Boston. Pp. 819; 199 illustrations and a colored plate. Philadelphia: Lea & Febiger, 1938. Price, \$10.00.

This book represents a logical sequel to *Theoretical Principles of Roentgen Therapy* edited by Dr. Pohle. The contributing authors have been selected for their aptitude in special branches of radiation therapy and their names are well recognized in this country and abroad. The use of Roentgen rays and radium in the treatment of disease is relatively new and hence there is scarcely another branch of medical practice which allows more controversy regarding the details of their application.

For a long time, leading radiologists have recognized the need for some standard of technique in order that the results of this form of therapy can be adequately studied. In our opinion, this text, which is the first of its kind to be published in this country, represents a workable basis for radiologists and students of radiology. It is true that each author has described those methods and doses which have proven safe and valuable in his own experience, and there are many controversial points which will occur to the individual reader. Nevertheless, this volume deserves a position in the library of every radiologist because of its broad scope and its pioneering efforts in the field of irradiation therapy.

The editor has made no attempt to divide the field of Roentgen and radium therapy. Where one or both of these forms of treatment are ordinarily used, the technique of application is considered as it would be in the usual course of clinical therapy.

A valuable feature of the text is the complete presentation of the subject matter. A discussion of the history, etiology, pathology, clinical symptomatology, diagnosis and prognosis is included for many of the diseases. Brief mention is made of those pathologic states which are not amenable to irradiation therapy or in which such treatment is contraindicated.

Each chapter covers thoroughly the diseases of different systems such as the blood and blood-forming organs, circulatory system, respiratory system, gastro-intestinal tract, genito-urinary system, nervous system and so forth. An adequate bibliography is supplied for each of the units of subject material.

The book should serve as an excellent reference because it presents a variety of information and wealth of material which is beyond the reach of the personal experience of any one radiologist.

G. C.

TUBERCULOSIS AMONG CHILDREN AND YOUNG ADULTS. By J. ARTHUR MYERS, PH.D., M.D., F.A.C.P., Chief of Medical Staff and Director of Tuberculosis Activities, Lymanhurst Health Center; Professor of Preventive Medicine, University of Minnesota. With Chapters by C. A. STEWART, M.D., PH.D., Clinical Professor of Pediatrics, University of Minnesota; and PAUL W. GIESSLER, M.D., F.A.C.S., Assistant Professor of Orthopedic Surgery, University of Minnesota. An Introduction by ALLEN K. KRAUSE, M.D., Lecturer in Medicine, Johns Hopkins University. Pp. 401; 71 illustrations. Second edition. Springfield, Ill.: Charles C Thomas, 1938. Price, \$4.50.

THIS is an enlarged, revised and greatly improved second edition of *Tuberculosis Among Children*, first published in 1930. The first of three parts begins with a review of research in tuberculosis during the past 8 years, then deals with the incidence, diagnosis, prognosis and treatment of tuberculosis in infancy. Both pulmonary and extrapulmonary tuberculosis are included and there is a special chapter on tuberculous meningitis by Dr. C. A. Stewart. The method of application and value of the tuberculin test and the value of history-taking, Roentgen ray examination and physical examination in diagnosis are emphasized.

In part two the author covers the field of tuberculosis in children from infancy to adolescence. The relatively benign character of the tuberculous lesions found in the lungs and the lymph nodes draining the lungs during this period of life is explained. The author regards primary infection as sensitization which places the subject in danger of serious tuberculosis in later life rather than as vaccination which results in enhanced resistance to tuberculosis. The incidence of tuberculous infection and of Roentgen ray lesions, the pathology, diagnosis, prevention and treatment of tuberculosis in childhood are discussed. There is also a chapter on tuberculosis of the bones

and joints by Dr. P. W. Giessler and one by Dr. Stewart on chronic non-tuberculous pulmonary disease.

In Part III the diagnosis and treatment of apical tuberculosis in adolescents and young adults is discussed. Methods of spread of tuberculosis in family groups by extrafamilial contact and among nurses and medical students are considered, and there are special chapters dealing with latent tuberculosis and the spread of tuberculosis from adults to children.

The book is well printed, easy to read and illustrations are much improved. There is an extensive bibliography at the end of each chapter which will be of considerable value to the student who wishes to study the work of various investigators for himself.

THE NEW INTERNATIONAL CLINICS. Vol. 2, N. S. 1 (Old 48th), June, 1938.

Edited by GEORGE MORRIS PIERSOL, M.D., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, Philadelphia.

With 18 Collaborators. Pp. 315; illustrated, also 1 colored plate. Philadelphia: J. B. Lippincott Company, 1938.

THE higher standard set with the initiation of the new series of this periodical is well maintained in this number. The "clinics," which now occupy less than one-fourth of the volume, are on live topics and by good men. The "original contributions" are also by distinguished authors and well done, though most are not original in the sense that new material or hypotheses are presented. Especially noteworthy is the detailed consideration by Horace Grey of Sacro-iliac Joint Pain—also the longest article of the lot. The volume concludes with a 20-page review of Regional Ileitis by Tumen.

E. K.

THE SPECIAL PATHOLOGICAL ANATOMY AND PATHOGENESIS of the Circulatory, Respiratory, Renal and Digestive Systems, Including the Liver, Pancreas and Peritoneum. By HORST OERTEL, Strathcona Professor of Pathology, Director of the Pathologic Institute, McGill University, and Pathologist-in-Chief to the Royal Victoria Hospital, Montreal, Canada. Pp. 640. Montreal: Renouf Publishing Company, 1938. Price, \$8.50, from T. H. McKenna, Inc., 878 Lexington Ave., New York City.

LIKE the author's earlier volume on "Outlines of Pathology," this is a refreshing variation from the conventional approach to the subject and is correspondingly provocative. The plan followed is an "orientation in these subjects by a critical review of older and present ideas. Emphasis is put on problems that arise out of the uncertainties and contradictions of current knowledge and beliefs. I differ in this method of presentation from many of my colleagues and from the usual manner of text-books, which adopt a more conclusive and somewhat dogmatic manner in order to furnish a firmer basis for the student's mind. The method which I have followed endeavors to stimulate critical judgment and further penetration. In my experience, the student of this generation is altogether too apt to accept things which he is taught as final and correct and to keep them in his mind as a standard fixed armamentarium."

Of course, one cannot eat one's cake and have it too; so that to students having their first contact with pathology emphasis on uncertainties and contradictions necessarily demands that there be less time spent on acquiring other important information. It all depends on striking the proper balance between the two, which I suppose all good departments of pathology strive for and only attain with varying degrees of success.

As indicated in the subtitle, important systems, such as the nervous, skeletal, hemopoietic, endocrines, are not considered. One wonders if there is another volume to follow or if the author feels that it is more important to cover at least some systems properly than to include these also. To be sure, the usual text attempts to straddle the double job of aiding in the teaching of students and of serving as reference books for the physician for the rest of professional life. Objections to such an attempt, however, must meet the counter objection that for obvious reasons few can have works like Henke and Lubarsch or even Kaufmann ever at hand; and there has been little available between them and the single volumes of Pathology textbooks, until Dr. Oertel's two volumes appeared. I suppose one solution of this difficulty might be that the average medical student should continue to buy one of the more conventionally arranged books; but be put in as close contact as possible with books like Oertel's, which would also serve the useful purpose of pointing out to teachers his point of view and aiding them in carrying it out.

At any rate, this swan song (Dr. Oertel having relinquished the Strathcona Professorship last July) will be warmly welcomed by thoughtful students of and teachers of pathology, who cannot fail to derive much profit therefrom.

E. K.

PHARMACEUTICAL LATIN. For Pharmaceutical, Medical, Dental, and Veterinary Students and Practitioners. By JACOB S. DORFMAN, Assistant Professor of Pharmacy, Columbia University College of Pharmacy, etc. Pp. 146; second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, \$2.00.

THIS little book is intended primarily for those who have had little or no elementary Latin, and for these it should prove extremely valuable. There are glossaries of terms and abbreviations used in prescription writing, Latin-English and English-Latin vocabularies, and a general index. The author apparently has had considerable experience with the needs of students, and has met them admirably.

C. S.

DIABETES INSIPIDUS AND THE NEURO-HORMONAL CONTROL OF WATER BALANCE. A Contribution to the Structure and Function of the Hypothalamico-hypophyseal System. By CHARLES FISHER, PH.D., W. R. INGRAM, PH.D., and S. W. RANSON, PH.D., M.D., Institute of Neurology, Northwestern University Medical School. Pp. 212 (lithoprinted); 171 illustrations and 26 tables. Ann Arbor: Edwards Brothers, Inc., 1938. Price, \$5.00.

THE greater part of this monograph is devoted to a detailed presentation of the authors' experiments on the mechanism of diabetes insipidus. Since most of the data have already been published in medical journals, the necessity of such full publication of the minutiae of their results is doubtful, although it is convenient to have these data collected in one place. The important contribution of the authors has been their demonstration that interference with the nerve supply of the pituitary gland by accurately placed hypothalamic lesions produces atrophy of the posterior lobe and a cessation of its hormone production. This permits a reconciliation of the supporters of a hypothalamic cause and those of a pituitary cause of diabetes insipidus. The authors are cavalier in criticizing evidence of their opponents, but their opinion is based on the most adequate body of experimental evidence which is available and will, in all probability, withstand future attack.

The shorter but perhaps the more useful portion of the monograph consists in the considerable body of literature, critically analyzed. Certain portions of this literature, notably that dealing with the interrelationships of the thyroid and adrenal glands, are still too confused to allow any precise conclusion, but that dealing with the site of formation of the posterior lobe hormones is ripe for summarization and is very lucidly treated. One might wish that the authors had not been quite so ready to adopt the hypothesis of a pituitary regulation of water diuresis as a corollary of their understanding of diabetes insipidus.

The format of the monograph is an interesting departure. The process is called "lithoprinting," presents the appearance of typewriting, and has been adopted in the interests of economy. With the exception of two of the larger tables it is very readable and the illustrations are excellently reproduced.

The monograph is recommended as a reference book to those who are interested in problems connected with diabetes insipidus. A. W.

DIE CHIRURGIE DES KROPFES. By HOFRAT DR. KARL URBAN, Vorstand der chirurgischen Abteilung und Leiter des Krankenhauses der Barmherzigen Schwestern in Linz, a.D. Pp. 112; 51 illustrations. Second edition, enlarged. Wien: Franz Deuticke, 1938. Price, Paper, M. 7; Bound, M. 9.

This monograph attempts to cover all the important factors in the treatment of patients with thyroid disease. Emphasis is placed on the management of the large non-toxic nodular gland. The preoperative preparation, operative technique and the handling of such early and late postoperative complications, as hemorrhage, tracheal collapse, cardiac failure, tetany, myxedema and recurrent nerve paralysis, are discussed. In a section on the malignant lesions of the thyroid Roentgen therapy is advocated. The final section deals with the management of thyrotoxicosis. For American surgeons this section is inadequate; there is not much in this monograph which cannot be found in any of a dozen volumes written in English. I. R.

EMERGENCY SURGERY. By HAILTON BAILEY, F.R.C.S. (ENG.), Surgeon, Royal Northern Hospital, London; Surgeon and Urologist, Essex County Council; Surgeon, Italian Hospital, etc. Pp. 852; 816 illustrations (many in color). Third edition. Baltimore: William Wood & Co., 1938. Price, \$14.00.

In this manual, to which the surgeon can turn in dealing with a surgical emergency, there are 53 chapters, covering every field of surgery including the surgical specialties. The illustrations are excellent but frequently do not have the proper legends attached. Figure 99 is not a continuous method of gastric suction drainage. Not only are the operations themselves discussed but many aspects of preoperative and postoperative treatment are given detail. Typing and cross-agglutination for blood transfusion, the preparation of solutions for intravenous use and many other details lacking in many surgical textbooks are included. A great deal of the material is presented in a didactic fashion and is thus easily available and rapidly read. One finds many rules and "Golden Rules" given in the various sections of the book; some of these are excellent, others debatable; and some merely platitudes. The use of "Labat's cardiac stimulant" immediately after giving neocaine for spinal anesthesia is an example. The fall in blood pressure with spinal anesthesia is due to the action of

the anesthetic on the sympathetic nerves controlling the peripheral vascular bed; it is not of cardiac origin except indirectly. The author uses the term "general peritonitis," which in this country we are using as an autopsy and not an antemortem diagnosis. The operative methods described are on the whole good; but the Mitchell method for covering a large defect of the scalp, as illustrated in Figure 480, seems to the Reviewer to be glaring exception. The previous editions have been well received and even though this edition has its shortcomings it is on the whole a well-compiled and written text and will be found exceedingly useful by many practitioners who wish to find in a single volume a discussion of the surgical emergencies.

I. R.

ADVANCES IN THE THERAPEUTICS OF ANTIMONY. By PROF. DR. PHIL. NAT. HANS SCHMIDT, PH.D., and F. M. PETER, M.D. With a Preface by PHILIP MANSON-BAHR, M.D., C.M.G., D.S.O., F.R.C.P. Pp. 257; 10 illustrations. Leipzig: George Thieme, 1938. Price, Paper, Rm. 18.00; Cloth, Rm. 19.50.

THIS monograph deals with the literature, up to the end of 1937, on the use of antimony compounds in human and veterinary medicine. Physicians who have not followed these recent developments may be surprised to learn of more or less striking successes achieved by newer antimony derivatives in visceral and cutaneous leishmaniasis, schistosomiasis, filariasis, granuloma inguinale, leprosy, and multiple sclerosis in man, as well as in bovine trypanosomiasis, canine leishmaniasis and filariasis, equine and canine ascariasis, and other parasitic diseases in animals. These clinical data are presented in the form of uncritical abstracts of original papers, but the authors' opinions are presented at the end of each section. There is a section of 7 pages, with separate bibliography, giving a summary of the chemical properties and syntheses of the newer preparations. The final 166 pages are devoted to abstracts of work on experimental infections.

As a summary of the literature this book should be very useful to specialists in tropical medicine, chemotherapy and pharmacology. One might wish that the authors had been freer with adverse criticisms.

C. S.

THE HEART IN PREGNANCY. By JULIUS JENSEN, PH.D. (In Medicine), University of Minnesota, M.R.C.S. (ENG.), L.R.C.P. (LOND.), Assistant Professor of Clinical Medicine, Washington University School of Medicine, etc. Pp. 371; 5 figures and 117 tables. St. Louis: The C. V. Mosby Company, 1938. Price, \$5.50.

THIS book is divided into three parts. The first deals with the effect of pregnancy on the normal heart, including the increase in cardiac work during pregnancy and the mechanism whereby the heart meets the increased demands of pregnancy. The second part, which is brief, deals with abnormal cardiac impulse formation during childbearing. The third part, covering about two-thirds of the book, deals with organic heart disease and pregnancy including sections on rheumatic heart disease and "the non-rheumatic heart diseases." Practically all the literature of any importance (and some of no particular importance) has been discussed. Considerable attention has been devoted to the older literature, as the author was interested in tracing the origins of current views.

The book reflects the enormous amount of work and the care required for its preparation. The author deserves the thanks of everyone interested in the subject. The book should be in the hands of all who have to deal with the problems of heart disease in pregnant women.

C. W.

THE CULTURE OF ORGANS. By ALEXIS CARREL and CHARLES A. LINDBERGH. Pp. 221; 110 illustrations (38 plates). New York: Paul B. Hoeber, Inc., 1938. Price, \$4.50.

"THE purpose of this book is chiefly to describe the technique of the cultivation of whole organs in the Lindbergh pump. The results of the experiments are mentioned only as a proof of the efficiency to the procedures used for keeping the tissues alive *in vitro*." Appropriately, then, 3 of the 9 chapters are by the junior author and devoted to mechanical details of the "Lindbergh pump," its assembly and operation, which has now been tested in over 1000 experiments by the authors and used in 7 other laboratories in this country and abroad. Dr. Carrel's contribution is a discussion of the purpose and history of the method, of perfusing media, preparation of organs and their behavior outside the body. A final unsigned chapter, which considers the significance of results thus far obtained and the future of the method, demonstrates that a new stage (first attempted almost as early as tissue culturing) has now been established in the study of living tissues outside the body. Progress in our knowledge of organ physiology by the use of this method is inevitable; the sum of its contributions is indeed unpredictable. E. K.

PROGRESSIVE RELAXATION. A Physiological and Clinical Investigation of Muscular States and Their Significance in Psychology and Medical Practice. By EDMUND JACOBSON, A.M., PH.D., M.D., Laboratory for Clinical Physiology, Chicago. Pp. 494; 89 illustrations and 10 tables. Revised edition. Chicago: The University of Chicago Press, 1938. Price, \$5.00.

It is encouraging to find a valid contribution to a long-neglected field appreciated to the extent of a second edition. The method has been carefully controlled by a convincing series of objective tests and the results estimated critically and conservatively. The major portion of the book consists in a clear description of methods, controls and results. In addition there are several chapters on theory. Of these, the strongest deals with emotion, the weakest with tonus and nervous regulation. The book should be read and applied by every neurologist, psychiatrist and neurophysiologist. G. McC.

HANDBOOK OF HEMATOLOGY. In 4 volumes. Edited by HAL DOWNEY, University of Minnesota Medical School, Minneapolis. Thirty-seven Contributors. Pp. 3136; 1448 illustrations, including 50 colored plates. New York: Paul B. Hoeber, Inc., 1938. Price, \$85.00 set.

THOUGH it must be admitted that a hematologist might easily lose his bearings in the enthusiasm generated by first contact with this magnificent publication, still we feel that there is little risk of overstatement in ranking it not only as the best and most up-to-date, authoritative statement of the subject that exists today in any language; but also as one of the very best of the more ambitious American medical publications of recent times. The medical world, and especially the American medical world, owes a great debt to the late Paul Hoeber, who fostered the creation of this work, to Paul B. Hoeber, Inc., the firm that has brought it to fruition, and to Dr. Downey and his 37 collaborators—who have labored so faithfully to present a comprehensive picture of this rapidly expanding field. It is perhaps anticlimactic to add that until now there has been no text in English that was to be compared with the extensive foreign works in this field, in spite of the considerable increase of interest in hematology in this country in recent years and the important position that it has assumed in medical science and practice.

This *Handbook* is apparently designed to give the hematologist, whether in being or in prospect, a presentation that will best equip him for progress in knowledge of blood cells in health and disease. This naturally postulates adequate attention to the fundamentals as well as to the practical phases of the subject, and no apology is made, or required, for including sections on comparative hematology, origin and relation of blood cells and so on. In fact, more than one-half the book is devoted to the basic phases of the subject. Technical methods are not included, nor is there any consideration of blood fluids, both of which are covered in the *Handbuch der Allgemeinen Hämatologie*, though none too closely connected with hematology as interpreted in this country. This permits about twice the space and detail for the ground that is covered by the American work than is occupied in the 4-volume German system. Many of the subjects are presented in monographic proportions: Isaac's opening chapter on "The Erythrocytes" requires 158 pages; Jaffé's "Reticulo-endothelial System," 300 pages; Klemperer's "Spleen," 168 pages; Jordan's "Comparative Hematology," 164 pages; "Tissue Culture," 116 pages. The practical side of hematology does not suffer, however: the various anemias, polycythemia, infectious mononucleosis, agranulocytosis, leukemia, lymphosarcoma, leukocytosis and leukopenia, the special hematologic features of infancy and childhood—all find adequate treatment.

Detailed consideration of such a monumental work would obviously be out of place here, nor could proper evaluation be attempted until familiarity has been acquired through long contact. The Reviewer is glad that he can truthfully say, however, that wherever he has delved in the subjects that specially interest him, he has found clear, interesting and accurate statements, strengthened by a rich bibliography for each chapter. The importance of the bibliographies is stressed by the editor in his Preface; in a reference work of this kind they are especially important. Another indication of the scholarly nature of the work is that all the references are "complete." All the more strange, then, that a general bibliography has not been included. Surely works on hematology as a whole and many of historical interest should be assembled at the beginning or end of the work, even though some may already be included in the special chapter bibliographies.

The 44 chapters, mostly by different authors, necessarily overlap somewhat in subject matter and this is a desirable feature in a work of this scope, as it permits presentation of opposing points of view. Thus in the perennial hematologic contest about the monophyletic or polyphyletic origin of blood cells and their possible transmutations, there is opportunity for both sides to be heard. Those who shudder at Bloom's presentation of the almost limitless transformations from one cell to another of the Maximow school (though he nobly admits the possibility of different explanations) can turn to Sabin and Doan for a more orderly contemplation of development of separate cell systems in the bone marrow.

The 4 volumes in the customary Hoeber dark blue present the attractive appearance that we have come to expect in Hoeber publications. The paper is excellent and this may be the reason for one of the few defects in the production. In one sense, at any rate, the work is ponderous—it weighs just under 10 kilos. Pity at least the poor female assistants who must carry the set back and forth in medical libraries, often up and down several stack floors! The pagination proceeds uninterruptedly through all 4 volumes as is customary in Hoeber's systems. Except for a paltry saving of space by omitting the word "volume" when referring to this or that page, the reasons for this method are still to be appreciated by the Reviewer. The inconvenience to the reader, however, is lessened in this instance by an announcement on the back strip of each volume of the

pages included in that volume. If this were in larger type it would be more useful still. The illustrations are numerous and are original, for the most part made for this publication, otherwise for the author of the chapter. They are well chosen, well executed and show what they are supposed to show without losing verisimilitude or vitality. The index is good but might be more extensive, to the advantage both of the reader and of the student using the work as a reference source. The necessarily high price will doubtless tend to limit the distribution to medical libraries, schools and the wealthier members of the profession. It would be unfortunate if this factor should seriously curtail the use of this splendid production. Everyone interested in hematology should have access to a copy somewhere; many who have become acquainted with its contents will then find it necessary to own their own set in spite of the high cost. In any case, the fortunate owner will find himself the possessor of what is not only the best work on hematology now extant, but one which will be the most authoritative statement on many topics for many a year to come.

E. K.

PRACTICAL OTOTOLOGY, RHINOLOGY AND LARYNGOLOGY. By ADAM EDWARD SCHLANSER, M.D., Colonel, Medical Corps, United States Army; Chief of the Eye, Ear, Nose and Throat Service, Letterman General Hospital, San Francisco, etc. Pp. 315; 81 illustrations. Philadelphia: Lea & Febiger, 1938. Price, \$4.50.

WRITTEN primarily as a text for Army medical officers, this book omits historical data, anatomy, physiology and detailed ~~microscopic details~~. The purpose of the author was to present material which is ~~of~~ the rational treatment of those complaints which are of routine occurrence in otolaryngologic practice. In covering the entire field of otorhinolaryngology in 315 pages with the inclusion of plastic surgery, bronchoscopy and mastoid surgery, the author has succeeded in condensing his material to an irreducible minimum. The volume will serve admirably as a reference work for those seeking clinical facts, but because of the necessity for brevity the discussion is often inadequate for the beginner and too elementary for the experienced rhinologist. The author has succeeded in presenting his material well and has accomplished the objectives which he has set for this volume. The illustrations are well selected to amplify the text.

H. S.

THE BIOLOGICAL STANDARDISATION OF THE VITAMINS. By KATHARINE H. COWARD, D.Sc., Reader in Biochemistry, University of London; Head of the Nutrition Department, Pharmaceutical Society of Great Britain. Pp. 227; 44 figures and 29 tables. Baltimore: William Wood & Co., 1938. Price, \$4.50.

As the title implies, the methods for standardization of vitamins discussed in this book are, for the most part, confined to procedures based on animal experimentation. The treatise is divided into two main parts and two appendices. In the first part (7 chapters—148 pages) are discussed the methods for the standardization of vitamins A, B₁, C and D. Also included in this part is a chapter on principles of biochemical methods, one on the choice and care of laboratory animals and finally a discussion on the interdependence of the vitamins. The need for the use of a standard of reference is stressed throughout.

In Part II (63 pages) 5 chapters are devoted to methods of statistical analyses and ways of determining the accuracy of each of the methods discussed in Part I. Appendix I is the report of the Second Conference on

Vitamin Standardization held in London in 1934. Appendix II is a series of tables giving the vitamin content (international units per gram) of various foods.

Throughout the monograph the author has drawn freely from her own vast experience in not only developing new methods but in critically evaluating methods developed by others. For those working in the field of vitamin standardization this publication can well become a handbook not only as a guide in conducting the experimental procedures but also in carefully and accurately interpreting and analyzing the results obtained.

J. J.

THE PHARMACOLOGICAL SHOCK TREATMENT OF SCHIZOPHRENIA. By DR. MANFRED SAKEL. With a Foreword by PROF. OTTO PÖTZL, Chief of the University Clinic for Neurology and Psychiatry of Vienna, Austria. Authorized translation by JOSEPH WORTIS, M.D., Research Fellow at the Bellevue Psychiatric Hospital of New York, and in Psychiatry at New York University Medical College. Pp. 136; illustrated. Revised English edition. New York: Nervous and Mental Disease Publishing Company, 1938. Price, \$2.75.

In 1930, G. Müller reported improvement in schizophrenics after epileptic seizures. In 1933, while using insulin to relieve withdrawal symptoms in drug addicts, the author observed that the periods of excitement in addicts and schizophrenics were similar; however, insulin had been used previously in the psychoses. In 1933, Meduna was producing camphor convulsions in guinea-pigs and, in 1935, reported success in the convulsant treatment of schizophrenics. Meduna now sponsors the convulsant treatment through intravenous injections of metrazol (cardiazol, the foreign term), a method that is less expensive and less difficult to apply. It is a question which method, insulin hypoglycemic comatose shock or metrazol convulsant shock, will prove the more successful.

Treatment with hypoglycemic shock should only be attempted by a trained physician, and in a well-equipped hospital; the author's equipment includes 19 separate items. The insulin method is considered in four phases: At first, daily doses of insulin are injected intramuscularly and minor mental changes may be noted. When severe hypoglycemic shock occurs—coma or epileptic attack—the second phase is entered upon. In the third phase, "rest-days" may be advisable. In the final or polarization phase, lasting only 5 or 8 days, but a small amount of insulin is administered. Some patients recover, some improve though they may relapse, and others are uninfluenced. Those treated soon after onset are the most hopeful, but improvement has been recorded after years' standing. While definite statistical data must await the future, nothing so stimulating has occurred in psychiatry since the induction of malaria in paresis, which also originated in Vienna.

N. Y.

THE FIGHT FOR LIFE. By PAUL DE KRUIF. Pp. 342. New York: Harcourt, Brace & Co., 1938. Price, \$3.00.

THOSE who object, as I do, to the unnecessarily lurid and inaccurate style of some of our dramatizers of medical science must nevertheless recognize the valuable service that they render in making the general public better acquainted with and more sympathetic to the methods and achievements of science. As his publishers state, de Kruif's "basic achievement to date has been to shorten the tragic—if not criminal—time lag between scientific discovery and the popular understanding that puts science to work." But any one who writes as well as the author surely does not have

to bolster his narrative with improbable profanity and exaggerated bitterness in order to make it "grip" and "thrill." As to the graver charge of inaccuracy that is often made against this type of book, I have read this one with this point in mind and am glad to say that, granting the limitations of an ordinary reader who has not attempted to check up on questionable assertions, I have detected no inaccuracies of importance (except for the contradictory statements on pages 127 and 133).

The book is based on articles that have appeared in recent years in *The Country Gentleman*, grouped in 4 major subjects, subdivided in 14 chapters. The first 6 deal with aspects of the campaign to lower infant and maternal mortality. Vivid pictures are painted of recent achievements, only too frequently to be balked by lack of sufficient funds to permit individuals, hospitals or health services to apply the discoveries made in a way that will produce maximum benefit for the public. The 4 chapters of Part 2 deal in similar style with poliomyelitis; Part 3 with tuberculosis; and Part 4 with syphilis, with a final chapter on sulphanilamide. Throughout runs the vein of the crippling insufficiency of funds, so that one should not be surprised to see the thesis emerge in the "Coda" that this is a fight to be waged by the whole people through their servants, the Public Health Service. Thus far the standpoint is at least debatable, though many would shudder at the results of abandoning all private initiative, and would question the staggering costs to an already financially embarrassed government. However, who can accept, if taken literally, the credo that follows: "The relief of suffering and the prevention of dying cannot be best served, for all, so long as there remains any money consideration between the people and the fighters for their lives. This reporter believes that all considerations of private profit are not only wasteful but infamous if they frustrate the fight for life, if they deny the right of one human being to live." The first sentence demands the thought *Honi soit qui mal y pense*, while the second suggests the lawyer's question, "Have you stopped beating your wife?" E. K.

A SYNOPSIS OF THE DIAGNOSIS OF THE ACUTE SURGICAL DISEASES OF THE ABDOMEN. By JOHN A. HARDY, B.Sc., M.D., F.A.C.S., El Paso, Texas. Pp. 345; 92 illustrations. St. Louis: The C. V. Mosby Company, 1938. Price, \$4.50.

THE author has very successfully attempted a synopsis of the diagnosis of acute abdominal diseases and has covered in his book a wide variety of lesions. After some general chapters on anatomy, general history-taking and physical examination he describes in turn the diagnosis of various traumatic and acute intra-abdominal lesions. His descriptions are brief and to the point, taking up in order the etiology, the history, the physical examination and various signs which are helpful in making the diagnosis. He describes the signs and symptoms and then gives a very complete discussion of the differential diagnosis. After discussing the acute surgical lesions of the abdomen the author has progressed to various chronic diseases of the abdomen and retroperitoneal lesions.

The subject matter is in general excellent, but the author devotes much space to signs which are unimportant and he often omits the discussion of the details of the disease which might be helpful. For example, in discussing the laboratory aids in diagnosing acute pancreatitis he mentions Elman's test for blood amylase as reliable and dependable but does not tell how this test is performed. The book would be more valuable if many of the signs were omitted and more details of the important diagnostic procedures were given. The text is well illustrated with line drawings.

On the whole the author has written a very useful book. It is published

in pocket size and is well indexed for easy reference. It should prove to be very useful as an easy reference for younger physicians and surgeons and would be a worth-while addition to the library of physicians who have to deal with acute abdominal diseases. L. F.

MANAGEMENT OF THE SICK INFANT AND CHILD. By **LANGLEY PORTER**, B.S., M.D., M.R.C.S. (ENG.), L.R.C.P. (LOND.), Dean, University of California Medical School, and Professor of Medicine, etc., and **WILLIAM E. CARTER**, M.D., Director, University of California Hospital Out-Patient Department, etc. Pp. 874; 94 illustrations. Fifth revised edition. St. Louis: The C. V. Mosby Company, 1938. Price, \$10.00.

THIS fifth edition of Porter and Carter's "Management" has been extensively revised and somewhat enlarged, since new material has been introduced into it. Especially has this enlargement been made in the treatment of the conditions seen in older children. Part I is devoted to well-condensed discussions of such general conditions as vomiting, fever, convulsions, etc. Part II is given to adequate treatment of diseases, though not in the typical manner of the usual textbook. Part III, that portion of the book which really follows the title, covers the management of every reasonably possible pediatric disease. This has always been a valuable and reliable source of information to hospital residents and the practising physician. It should be especially useful to the man practising general medicine who is seeking up-to-date information about pediatric treatment.

E. T., JR.

A HISTORY OF WOMEN IN MEDICINE. From the Earliest Times to the Beginning of the Nineteenth Century. By **KATE CAMPBELL HURD-MEAD**, M.D. Pp. 569; illustrated. Haddam, Conn.: The Haddam Press, 1938. Price, \$6.00.

LIKE so many worth-while medical projects of the past generation, this work was inspired by Osler and the group at Johns Hopkins interested in the history of medicine. For more than 40 years, but especially after giving up her Connecticut practice in 1925, the author has pursued her subject by personal interview and correspondence and study of original documents in the great libraries of this country and Europe. The present volume is the first fruit, carrying the narrative from the earliest times to the beginning of the 19th century. It is hoped that the story will be completed in a second volume.

The 10 chapters follow a chronologic order. The part played by women in primitive medicine, among the Egyptians, Hebrews, Greeks, Romans, carries us in the first chapter of 70 pages to the 2d century A.D. After a chapter on the early Middle Ages and one on Trotula and the School of Salerno, there is one chapter devoted to each century. We see the earliest known representation of a woman physician (3000 B.C.)—a priestess, to be sure; women physicians of the early Christian era; the rôle of the housewife and the noblewoman, and of nuns and midwives, in the treatment of the sick through the centuries; women teaching anatomy (the prosector in the famous Mundinus frontispiece is a woman); women operating and assisting in operations; and famous individual medical women too numerous to mention. Inclusion of an adequate background swells the picture to a fairly complete history for the general reader.

The narrative is well documented, the illustrations good—illustrative and well executed—and the format pleasing, without being lavish.

This important work, an industrious and competent study of a formidable

subject that has hitherto been comparatively neglected, will be of interest to all those concerned with the history of medicine, will be of value as a reference book, and should be owned by intelligent women who have enough pride in their sex to wish to be familiar with some of its accomplishments.

E. K.

A TEXT-BOOK OF PATHOLOGY. An Introduction to Medicine. By WILLIAM BOYD, M.D., LL.D., M.R.C.P. (EDIN.), F.R.C.P. (LOND.), DIPL. PSYCH., F.R.S.C., Professor of Pathology and Bacteriology in the University of Toronto, Toronto; formerly Professor of Pathology in the University of Manitoba, Winnipeg. Pp. 1064; 459 illustrations and 16 colored plates. Third edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, \$10.00.

In the third edition of this popular text there is a thorough revision of the contents with an added wealth of new material. The latter includes tuberculosis of the stomach, lymphadenoid goiter, uteroplacental apoplexy, plasma-cell mastitis, Brenner's tumor, dermatomyositis, regional ileitis, meconium ileus, adenoma of bronchus, congenital arteriovenous fistula and adenolymphoma of salivary glands.

Appreciating the difficulty of correctly describing the gross appearance of organs, the author has included a descriptive outline of each organ in a state of health. This new feature should add considerably to the value of the book for the student of pathology.

The generous discussion of virus diseases has been rewritten and the virus diseases of the central nervous system have been grouped together.

The book is rich in illustrations and each chapter is followed by a list of carefully selected references for additional reading.

The third edition should only further increase the well-merited popularity this textbook has won for itself in its first and second editions. D. C.

EMBRYONIC DEVELOPMENT AND INDUCTION. By HANS SPEMAN, Professor Emeritus of Zoölogy, University of Freiburg im Breisgau. Pp. 401; 192 illustrations. New Haven: Yale University Press, 1938. Price, \$5.00.

THIS is the written version of the latest series of lectures delivered at Yale University on the Silliman Foundation. The subject matter is the physiology of development, as studied by special experimental methods. The particular questions considered are whether the larger partial processes of development are connected among themselves, whether one causes and conditions the others or whether they proceed side by side, independent of each other. Two main experimental procedures have been used—isolation of a portion of the organism, the independent development of which is then followed, and transplantation of small portions to other regions of the embryo, where the transplants develop in a new environment. An important technical aid is the vital staining of small parts of the living embryo with a harmless stain, such as Nile blue or neutral red. The color, applied by a minute piece of dyed agar laid upon the part, remains in the cells for many days. By this means the derivatives of small areas are followed through their further development, and the loci of future organs can be seen in the early gastrula. The isolation experiments include the separation of the first blastomeres, the isolation of cell fragments and the division into parts of very early stages of the embryo, as first carried out by Roux and Driesch.

The book represents the author's life work, and in it are illustrated

many of the concepts of experimental embryology which he has originated or added to, such as organizers, centers of organization, regulation, potency and determination. He cannot persuade himself that the gradient theory, in the sense of Child, applies to the early development of the amphibian egg.

W. A.

DATA ON THE GROWTH OF PUBLIC SCHOOL CHILDREN. (From the Materials of the Harvard Growth Study.) By WALTER F. DEARBORN, Professor of Education and Director of the Psycho-Educational Clinic, Graduate School of Education, Harvard University, JOHN W. M. ROTHNEY, Instructor in Education and Research Associate at the Psycho-Educational Clinic, Graduate School of Education, Harvard University, and FRANK K. SHUTTLEWORTH, Assistant Professor of Education, Department of Education, and Research Associate, Institute of Human Relations, Yale University. Vol. III, No. 1 (Serial No. 14). Pp. 136. Price, \$1.00.

A HANDBOOK OF METHODS FOR THE STUDY OF ADOLESCENT CHILDREN. By WILLIAM WALTER GREULICH, PH.D., HARRY G. DAY, SC.D., SANDER E. LACHMAN, M.D., JOHN B. WOLFE, PH.D., FRANK K. SHUTTLEWORTH, PH.D. Vol. III, No. 2 (Serial No. 15). Pp. 406; 30 illustrations. Price, \$2.25.

THE ADOLESCENT PERIOD. A Graphic and Pictorial Atlas. By FRANK K. SHUTTLEWORTH, Institute of Human Relations, Yale University. Vol. III, No. 3 (Serial No. 16). Pp. 246; 458 illustrations. Price, \$2.00. Monographs of the Society for Research in Child Development. Washington, D. C.: Society for Research in Child Development, National Research Council, 1938.

THIS volume (No. 1) represents the detailed protocols of a series of 11 or more annual physical and mental measurements of 747 boys and 806 girls. The methods used in these examinations and an annotated bibliography of the Harvard Growth Studies is included.

No. 2 is a very useful handbook. It contains a mine of new and revised information on many aspects of the physical structure and function of the adolescent. It considers such subjects as metabolism, circulation, respiration, posture, blood, urine, skin, bones, puberty, sexual behavior, intelligence, special interests and abilities and a large number of other body properties. These are briefly stated and leading references mentioned. This monograph will be a useful aid to physicians and educators dealing with the adolescent boy or girl.

No. 3, a companion volume to No. 2 of this series, consists entirely of annotated charts and photographs on such subjects as growth, metabolism, sexual maturation, health, intelligence, education, interests and attitudes, behavior problems, sexual adjustments and occupational adjustments. In graphic form, its information is easily and quickly referred to, and has a good index. It is also a very useful handbook for ready reference for the teacher or physician at a secondary school.

J. S.

THE DOCTRINE OF SIGNATURES. A Defense of Theory in Medicine. By SCOTT BUCHANAN. Pp. 201. New York: Harcourt, Brace & Company, 1938. Price, \$2.75.

THIS discourse, by one who has been concerned with philosophy for many years and with medicine for 2 years, will prove to be beyond the sympathetic understanding of some readers. The realm of medicine has undergone immense expansion. As an instance: formerly, mental diseases occupied but small space; today, in addition, psychiatry includes mental

hygiene, psychoanalysis, the psychoneuroses, child guidance, together with some understanding of criminology. Though knowledge of the greatest importance has been revealed through accident, such "luck" cannot be relied upon to provide advancement, so that theories must precede the establishment of most facts. But with such an array of work before us, little time remains for theorizing.

The author believes coöperation between practical medical men and philosophers competent to theorize would supply the answer, and offers a plan. Buttressing his contentions with the dogmas of such philosophers as Galen, Plato and Hippocrates, some of the proposals are as follows: "A critical evaluation of the sciences upon which the medical arts depend with special attention to their past uses and their possible future relevance to an integrated science of physic;" "A digest of current working hypotheses, instruments, and techniques in medical research and practice;" "A study of measurement in science, numerical and non-numerical;" "A study of medical casuistry, epidemics, preventive medicine, creative medicine, and the proposed agencies for the medical control of society and the social control of medicine;" "A study of the possibilities of a permanent board for the continuous criticism and codification of medical knowledge." Does this ambitious program of the philosopher hold the answer to some of the grave problems confronting the medical profession? N. Y.

THE PITUITARY GLAND. An Investigation of the Most Recent Advances. The Proceedings of the Association, New York, December 28th and 29th, 1936. (Association for Research in Nervous and Mental Disease, Vol. XVII of a Series of Research Publications). Editorial Board: WALTER TIMME, ANGUS M. FRANTZ and CLARENCE C. HARE. Pp. 764; 160 illustrations, 6 plates and 53 tables. Baltimore: The Williams & Wilkins Company, 1938. Price, \$10.00.

THIS is an excellent collection of papers by those (46 authors writing 42 chapters) who are actively working on the anatomy, physiology, and clinical disorders of the pituitary. By far the largest number of papers deal with experimental investigations and with theoretical, rather than clinical, aspects.

This mode of presenting recent work on the pituitary, by numerous authors, seems a particularly desirable one. Too many books on endocrinology are biased by a single author's interpretation of the literature covering aspects of the problems beyond the sphere of the author's personal investigations. But in this symposium, the present status of the pituitary is more fairly represented by the differing opinions and interpretations between the various authors who are discussing only the fields of their special interests.

A few of the clinical papers have faults common to clinical endocrinology. On the whole, however, it is a very interesting volume for those who want to examine critically the evidence upon which present conceptions of pituitary physiology are based. I. Z.

THE CONSTRUCTION OF VULCANITE APPLICATORS FOR APPLYING RADIUM TO LESIONS OF THE BUCCAL CAVITY, LIPS, ORBIT AND ANTRUM. By DESMOND GREER WALKER, M.A., M. DENT. Sc., M.B., B.Ch., Assistant Dental Surgeon to the Royal Dental Hospital; Dental Registrar at the Middlesex Hospital, etc. Foreword by W. WARWICK JAMES, O.B.E., F.R.C.S., L.D.S. Pp. 61; 2 illustrations and 22 plates. London: John Murray for the Middlesex Hospital Press, 1938. Price, 5/-.

THIS monograph is the result of several years of experience gained in the construction of appliances to be used for topical applications of radium from the Radium Department of the Middlesex Hospital. The first por-

tion of the book concerns itself with a brief discussion of the more elementary aspects of radium physics. Since the monograph was apparently written for dental surgeons, this discussion helps considerably to crystallize the problems pertaining to surface radiation therapy. The remaining portion of the book deals with the construction of vulcanite applicators. The author prefers the term "vulcanite applicator" to the term "dental applicator" because the former term implies the material from which the applicators are made and does not suggest that their use is limited to lesions within the mouth. The author discusses in detail the various methods for obtaining impressions of lesions. He also discusses fully the question of impression material to be used for different lesions. Each step in the actual construction of the vulcanite applicators is carefully considered, described, and clearly illustrated. The discussions included in this monograph are not limited to the dental applicators. It also includes data, photographs, and directions for the construction of vulcanite applicators for lesions of the lips, orbit and antrum.

P. H.

NEW BOOKS.

Meningiomas. Their Classification, Regional Behaviour, Life History, and Surgical End Results. By HARVEY CUSHING, M.D., Sometime Associate Professor of Surgery, Johns Hopkins University; Moseley Professor of Surgery, Harvard University, and Surgeon-in-Chief, Peter Bent Brigham Hospital, Boston, etc. With the Collaboration of LOUISE EISENHARDT, M.D., Assistant Professor of Pathology, Yale University, School of Medicine; Formerly Associate in Surgery, Peter Bent Brigham Hospital, Boston. Pp. 785; 685 illustrations. Springfield, Ill.: Charles C Thomas, 1938. Price, \$15.00.

Biochemistry for Medical, Dental and College Students. By BENJAMIN HARROW, Ph.D., Chemistry Department, City College, College of the City of New York. Pp. 383; 52 illustrations. Philadelphia: W. B. Saunders Company, 1938. Price, \$3.75.

Die Lehre von der Vitalförmung. By PROF. DR. K. KIYONO, Direktor des Pathologischen Institutes der Kaiserl. Universitaet, Kyoto, PROF. DR. S. SUGIYAMA, Pathologisches Institut der Medizinischen Fakultät, Kanazawa, and DOZ. DR. S. AMANO, Pathologisches Institut der Kaiserl. Universitaet, Kyoto. Pp. 577. Kyoto, Japan, 1938.

The New International Clinics, Vol. 3, New Series 1 (old 48th), 1938. Edited by GEORGE MORRIS PIERSOL, M.D., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, Philadelphia. Pp. 341; illustrated. Philadelphia: J. B. Lippincott Co., 1938.

A symposium of four articles on sulphanilamide is combined in this volume with a score or more of original contributions, six clinics and a review of pyelitis in pregnancy.

Laboratory Manual of Hematologic Technic. Including Interpretations. By REGINA COOK BECK, M.A., M.D., Formerly Instructor in Pathology and Bacteriology at George Washington University Medical School; Head of the Department of Bacteriology, William and Mary College Extension, etc. With a Foreword by FRANK W. KONZELMANN, M.D., Professor of Clinical Pathology, Temple University, Philadelphia. Pp. 389; 79 illustrations. Philadelphia: W. B. Saunders Company, 1938. Price, \$4.00.

Handbook of Histological and Cytological Technique. By R. R. BENSLEY and S. H. BENSLEY, Department of Anatomy, The University of Chicago. Pp. 165. Chicago: The University of Chicago Press, 1938. Price, \$2.00.

The Chemistry of the Amino Acids and Proteins. Edited by CARL L. A. SCHMIDT, M.S., PH.D., Professor of Biochemistry, University of California. Pp. 1031; 259 illustrations and 144 tables. Springfield, Ill.: Charles C Thomas, 1938. Price, \$7.50.

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PROGRESS OF MEDICAL SCIENCE

THERAPEUTICS.

UNDER THE CHARGE OF

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CERTAIN BIOLOGIC ACTION AND THERAPEUTIC EFFECTS OF MORPHINE AND OF RELATED COMPOUNDS.

MORPHINE is one of the most useful drugs. In China, the use of opium dates back as far as the recognition of cholera there. The stalk of the poppy plant is mentioned as an ingredient of an Egyptian prescription in the Papyrus-Ebers.³ The juice of the poppy was certainly an effective remedy in the hands of physicians of ancient Greece. Pliny was probably the first to use the word "opium."¹⁰ During the centuries immediately following, some progress was made in the effective use of opium preparations. The first milestone in this field, however, is the contributions of the young German pharmaceutical apprentice, Sertürner, who in a series of reports published between 1805 and 1817 described the isolation and certain chemical and pharmacologic characteristics of morphine.¹⁰ Thereafter, as a result of the development of organic chemistry, experimental pharmacology and clinical medicine, valuable information was acquired concerning the chemistry and the biologic action of morphine and of some related compounds. In recent years, after a period of relative stagnation, interest in this field has been renewed. An analysis of some of the new contributions is of significance to physicians, not only because they are of practical value, but also because they constitute an example of the way in which knowledge often progresses in biologic sciences, including clinical medicine.

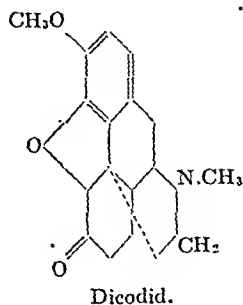
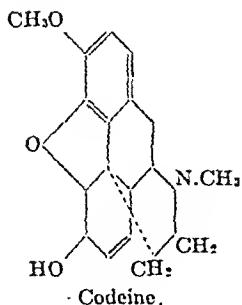
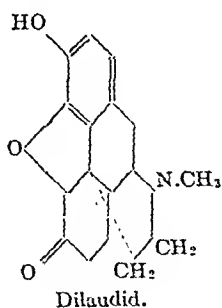
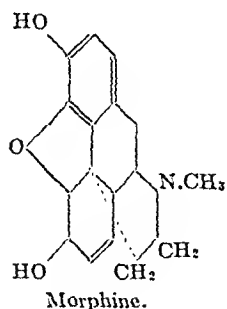
Chemical and pharmacologic contributions of recent years demonstrate that chemotherapy, in spite of skepticism on the part of some, has yielded a number of useful therapeutic agents. The work accomplished in the field of the alkaloids of the morphine derivatives serves as an example of the usefulness of such chemotherapeutic investigations in medicine. This may be added to other recent important chemotherapeutic advances, such as the discovery of the sulphanilamide group in the treatment of bacterial and other infections, of carbasone in amebiasis, of carbon tetrachloride, tetrachlorethylene and hexylresor-

cinol groups as anthelmintics, of the barbituric acid derivatives with varying persistence of action and side effects, of substances related to epinephrine and ephedrine with different peripheral and central actions, of the physostigmine group with good therapeutic effects on the smooth and striated muscles, of the cocaine group as local anesthetics, of various gases as general anesthetics, and of several other useful drugs.

The main efforts in the study of alkaloids of the morphine group may be divided into (1) the preparation of new compounds through systematic alteration of the chemical structure of the morphine and codeine molecules, with the primary purpose of obtaining drugs having one or more of the specific *therapeutic* effects of morphine but without its side effects; and (2) further pharmacologic studies of morphine and other alkaloids of opium in order to elucidate problems unsolved in the past.

I. Some of the New Morphine Derivatives. The purposeful alteration of the morphine and the codeine molecule is a relatively simple procedure. The primary hindrance to progress lies in the fact that the biologic and therapeutic assay of each compound prepared by the chemist is laborious and difficult.

From the study of the alkaloids of opium, such as morphine, narcotine, papaverine, codeine, narceine and thebaine we have known for some time that a relatively slight change in the chemical composition may alter significantly the pharmacologic action and therapeutic effects. Among the numerous new alkaloids with possible therapeutic effects *dilaudid* and *dicodid* have been studied rather extensively, both in animals and in man. *Dilaudid* is an isomer of morphine, *dihydro-morphinone*, while *dicodid* is an isomer of codeine, *dihydrocodeinone*:



Dilaudid has been used in Germany since 1926 and in this country since 1932. Its biologic properties, including its analgesic and respiratory action, are quite similar to those of morphine. It has been claimed, however, that it exerts less effect on the gastro-intestinal canal than morphine. Nausea and vomiting are less often observed and constipation is less severe. An analysis of the literature by Eddy indicates that doses smaller than those of morphine are clinically more effective but also more toxic.^{4a} The ratio between effective doses of morphine and of *dilaudid* for the production of desirable therapeutic effects differs very little from that between their toxic doses. While tolerance to *dilaudid* develops less easily than tolerance to morphine, nevertheless addiction has been reported. In his review Eddy expressed the opinion that, although the clinical reports are on the whole favorable, final evidence concerning addiction to *dilaudid* is still lacking. In using *dilaudid* one should remember that it is a potent morphine derivative. As a substitute for morphine, its use, as has been pointed out,²¹ is particularly indicated in the presence of pain in patients with neoplastic diseases, in cases of obstinate cough, in pulmonary tuberculosis and in coronary disease. It can be administered orally, rectally, subcutaneously or intravenously. Following oral administration it is absorbed rather rapidly and the duration of the action is about 3 hours, which is less than that of morphine. When applied in suppositories its absorption is slower and hence its effect is more lasting. The average therapeutic dose is from 2 to 2.5 mg. ($\frac{1}{30}$ to $\frac{1}{20}$ grain). Factors (pain, anemia, and so forth) which influence the effective dosage of morphine also influence that of *dilaudid*. The manifestations and treatment of *dilaudid* intoxication are essentially identical with those of morphine intoxication. It has been stated: "While *dilaudid* offers some advantages over morphine under special indications, the optimistic expectation and careless use that followed its earlier clinical trial are not justified."²¹

The pharmacologic and therapeutic properties of *dicodid* (*dihydrocodeinone*) have been summarized by Sametinger.¹⁶ As judged from observation on animal and on man, in its action *dicodid* stands between codeine and morphine. Its respiratory depressant and sedative effects are claimed to be more marked than those of morphine; its narcotic and analgesic effects are less. In man it produces euphoria. *Dicodid*, in contrast to morphine, does not cause constipation. Side effects, such as nausea, vomiting and excitement, may develop even after an average-sized dose. The tendency to addiction after its prolonged use is less than after morphine, but addiction does occur. It is less severe, however, than that following morphine, and hence can be treated more effectively. Sametinger describes two instances of addiction as a result of which the patients broke into the medicine closet of the hospital ward. Addicts have used daily from 20 to 25 tablets of 10 mg. ($\frac{1}{6}$ grain) each. The average therapeutic dose of *dicodid* is 5 mg., which is equivalent to about 30 mg. of codeine. For oral use a 5 ($\frac{1}{12}$ grain) or 10 mg. ($\frac{1}{6}$ grain) tablet of the bitartrate salt is administered. A single oral dose of 20 mg. ($\frac{1}{3}$ grain) should never be exceeded. The dose is usually repeated 2 or 3 times daily. When used subcutaneously, 7 or 15 mg. of the hydrochloride are administered from 1 to 3 times in 24 hours. The average dose for children under 1 year of age is 1 mg. ($\frac{1}{60}$ grain), and for children above this age 2 mg. ($\frac{1}{30}$ grain).

Sametinger¹⁶ has analyzed the toxic reactions of dicodid on the basis of 30 cases. Mental confusion may develop even after an average therapeutic dose. Excitement may occur, particularly in women and in children. In more severe intoxication deep sleep may last as long as 3 days. One fatality occurred in a 2-year-old child who received 5 mg. ($\frac{1}{12}$ grain), i. e., 5 times the single dose for children. A 4-year-old child suffered from circulatory collapse after receiving 3.7 mg. ($\frac{3}{16}$ grain). The analysis of the cases indicates a wide variation in individual susceptibility. It is worth pointing out that in 6 men no toxic manifestations occurred even after doses as high as 200 mg. (3 grains).

Schürch and Brunner¹⁷ report on the therapeutic effects of *dihydrodcsoxymorphine D* as observed in 900 surgical cases. This substance, according to these observers, has a rapid analgesic but a slight narcotic effect. The height of action was reached within 10 or 15 minutes, which is sooner than with morphine. Its sedative effect is claimed to be better than that of morphine. It is claimed also that unpleasant side effects referable to the gastro-intestinal canal and to the bladder are less pronounced than with morphine. Addiction, when it developed, was manifested in slight craving. This substance was used in combination with atropine in premedication for surgical anesthesia, and was found useful in the relief of pain in the daytime, when sleep is not desirable. Caution is advised in its use in cases with head injuries. For surgical premedication the usual dosage was 2 mg. ($\frac{1}{30}$ grain), injected subcutaneously. Depending on the severity of pain its effect lasted from 30 minutes to 6 hours, with an average of 2 or 3 hours. In cases with severe pain such a dose was repeated as often as 8 times in 24 hours. (The therapeutic usefulness of this preparation cannot be considered established as yet, in the opinion of the writer of this review.)

Various effects of *dilaudid* have been compared with those of *morphine*, *heroine* and *codeine* by Seevers and his associates. Tatum, Seevers and Collins²⁰ have demonstrated that a condition closely portraying human addiction could be arrived at in the monkey (*Macaca mulatta*). The superiority of the monkey to other laboratory animals as a test object for the study of addiction has been confirmed by a number of observers. More recently Seevers^{18a} has again demonstrated the superiority of the monkey for the comparative study of addiction to the opium derivatives. He has concluded that the rapid method of addiction in monkeys is satisfactory for the determination of the relative addictive potentialities of a series of opium derivatives, although this test does not give quite so clear a differentiation as that following a more prolonged period of poisoning, such as occurs in the human addict.

Using the monkey as an experimental animal Seevers^{18b} compared the tendency to addiction to *dilaudid* with that to *morphine*, *heroine* and *codeine*. In monkeys, the signs of withdrawal with *dilaudid* were less severe than with *morphine* when the two drugs were used in a ratio of dosage of 1 to 5, as commonly used in the clinic. The signs of withdrawal were most severe with *heroine* and *morphine*. The convulsant action of *codeine* in the monkey prevented the attainment of doses which were comparable to those of the other derivatives. Since the lethal dose of *dilaudid* for the monkey was not determined, the study does not serve for a comparison of these drugs in relation to tolerance or to an elevation of the lethal dose.

Seevers emphasizes the fact that all the opiates studied are potentially capable of producing addiction provided a large enough dose is maintained over a long period of time. "It would be incorrect to speak in terms of addiction, or no addiction, as regards the action of any of the opiates known at the present time." He questions whether a derivative of morphine will ever be found which lacks all the undesirable qualities of morphine. He believes that the evidence so far indicates that narcosis or subjective depression involves an action upon a different mechanism than that responsible for the production of analgesia. The group of cells which is concerned in the narcosis of the drug is, in Seevers' opinion, also responsible in a large measure for the production of abstinence symptoms. Obviously the most desirable derivative would be one which has a potent analgesic action and which at the same time produces a minimum subjective depression or narcosis.

Subsequently Seevers and Pfeiffer¹⁹ conducted a study of the analgesia, subjective depression and euphoria produced by morphine, heroine, dilaudid and codeine in normal human subjects. They rightly point out that the information available in the literature concerning analgesia is based for the most part on statistical studies of clinical data or on personal opinion of drug efficiency. Macht, Herman and Levy¹¹ have studied certain pharmacologic characteristics of six principal natural alkaloids of opium. It is, however, difficult to draw conclusions of a quantitative nature from their work. Seevers and Pfeiffer¹⁹ have utilized the v. Frey technique in establishing the average pain threshold on five sensitive face spots. The procedure is apparently applicable in a reasonably quantitative manner to the study of the rapidity of onset, intensity and duration of analgesia produced by drug action in the normal human subject. In 8 subjects the effects of both subcutaneous and intravenous injection of morphine, heroine, codeine and dilaudid have been studied with regard to analgesia, subjective depression, euphoria and side action. The subcutaneous doses of the four drugs which produced a comparable elevation of the pain threshold were as follows: Morphine sulphate, 10 mg. ($\frac{1}{6}$ grain); heroine hydrochloride, 1 to 2 mg. ($\frac{1}{60}$ to $\frac{1}{30}$ grain); dilaudid hydrochloride, 0.8 to 1 mg. ($\frac{1}{60}$ grain); codeine phosphate, 64 mg. (1 grain). The following is the order of potency of these drugs on the basis of the dosage used: *Duration of action*: morphine, dilaudid, codeine and heroine. *Duration and intensity of subjective depression*: morphine, dilaudid, heroine and codeine. *Euphoria*: heroine, morphine, dilaudid and codeine. *Side action*: morphine, dilaudid, codeine and heroine.

The average time interval which elapses after subcutaneous injection of the four drugs before the maximum elevation of the pain threshold occurs is as follows: Heroine, 30 minutes; codeine, 30 to 60 minutes; morphine, 60 to 90 minutes; dilaudid, 90 minutes. After intravenous injection the peak of analgesia occurs at 20 minutes with all four drugs. The variations between subcutaneous and intravenous administration result primarily from differences in the rate of absorption from the skin area. Intravenous differs from subcutaneous administration of the doses used of the four drugs as follows: (1) A less pronounced and less prolonged elevation of the pain threshold occurs; the rise is relatively the same with morphine, dilaudid and codeine, whereas heroine is almost as effective as if given under the skin. (2) Greater subjective depression

is present for a short period and there is less euphoria. Since no absolute correlation was found between analgesic action and narcosis, these authors concluded that two different mechanisms are involved in these effects.

Simultaneously with these studies other efforts have been made to find useful therapeutic agents through changes in the morphine molecule. The practical applicability of the results cannot be evaluated as yet. Of these investigations, a few will be mentioned as examples. Wright and Barbour²² studied the changes in the physiologic properties and particularly in the respiratory effects of morphine brought about by shifting the position of the alcoholic hydroxyl group and removal of the aliphatic double bond by hydrogenation. Rotation of the 6-carbon hydroxyl in one instance (morphine to α -isomorphine) reduces slightly the activity of the drug. The same change in the hydrogenated derivatives (dihydromorphine to dihydro- α -isomorphine) has little or no effect if judged over the complete dose range studied, but reduces the activity if the drugs are compared as to their minimum effective doses. A similar qualitative relationship exists between the codeine and dihydrocodeine isomers with the exception of dihydroallopseudo-codeine, which is considerably less effective as a respiratory depressant than dihydroisocodeine. The variations in minimal subcutaneous doses of different compounds required to depress the respiratory mechanism of the rabbit have been determined.

The toxicity, analgesia, depressant action and intestinal action of the isomers of morphine and dihydromorphine have been studied by Eddy.^{4b} The main conclusion of his study is that the pharmacologic relationships afford a basis for pairing the isomers, while pairing by chemical means is not possible at present.

Twelve compounds derived from morphine and dihydromorphine by substitution in the 6-carbon position have been investigated recently by Wright and Barbour.²² The substitution involved a replacement of the 6-carbon (alcoholic) hydroxy group by acetyl, ketone, hydrogen, halogen, methoxy and ethoxy groups. Unanesthetized rabbits were used. The respiratory rate, oxygen consumption and response to a carbon dioxide air mixture were determined before and 1 hour after subcutaneous injection of the drug. The most striking and obvious result was that substitution in the 6-carbon position has in each of 12 compounds caused a considerable increase in the potency of the molecule as a respiratory depressant. The one change common to all of the substitution was the loss of the alcoholic hydroxyl group. Alpha-mono-acetylmorphine was found to be one of the most depressant of the morphine derivatives. Comparison was also made between the derivatives of morphine and dihydromorphine in order to determine the effect of hydrogenation in the 6-7 and 7-8 carbon position. Hydrogenation in the 6-7 or 7-8 carbon position of the derivatives of morphine had no significant effect on the potency in 6 cases, caused a definite decrease in 2, an increase in 2 and an increase only at the higher dose range in 1. Hence the results of such hydrogenation are not predictable.

It has been stated⁵ that besides the phenanthrene skeleton and the basic group an especially characteristic feature of the morphine molecule is the peculiar oxygen bridge which forms a partly hydrogenated furan ring within the phenanthrene skeleton. Henecka⁸ therefore

undertook a study to ascertain whether simple, basic substituted furan derivatives without phenanthrene structure also possess a morphine-like action. This investigation shows that the linkage of a hydrogenated keto- or hydroxy-furan ring with one or more basic radicals does *not* lead to compounds with pharmacologic properties resembling those of morphine.

II. Some Recent Contributions on Pharmacologic Action and Therapeutic Effects of Morphine and Related Compounds. Notwithstanding the fact that morphine has been studied extensively by pharmacologists and clinicians, there are a number of obvious problems of importance in the daily practice of medicine which are still unanswered or inadequately understood. The dosage, particularly in children, the alleged contraindications of the drug in certain types of heart disease, pulmonary diseases, severe anemia, cirrhosis of the liver, peritonitis, intestinal distention, head injuries and cerebrovascular accidents are problems as yet unsettled. The main reason for lack of established knowledge in these questions lies in the fact that either there is discrepancy between observations in animals and studies on diseased man, or no well-controlled observations have been made on man. There are available a few studies made in recent years which help to clarify some of these problems.

Dosage in Children. Irish⁹ reports a critical study, based on 297 observations, on the dosage of camphorated tincture of opium and morphine in infants. He points out the confusion in dosage as indicated by statements in textbooks. The average effective therapeutic dose of the tincture in cases of colic and diarrhea was found to be 5 minims per pound of body weight. The dose of morphine for diarrhea was 0.12 mg. ($\frac{1}{500}$ grain) per pound; for pain 0.15 mg. ($\frac{1}{400}$ grain) per pound by mouth or 0.1 mg. ($\frac{1}{600}$ grain) hypodermically. Such doses may be repeated in 4 hours. For convulsions, drugs other than morphine should be used. A corresponding amount of the drug, as indicated by the degree of drowsiness, exerts on infants under 4 months slightly more effect than on those over 4 months of age. Full physiologic effects without signs of toxicity were elicited with morphine sulphate in doses of 0.1 mg. ($\frac{1}{600}$ grain) per pound. This dosage is about the same in relation to weight as the dosage for adults, and it is far below the toxic dose of 0.43 mg. ($\frac{1}{250}$ grain) per pound. Susceptibilities of varying degree were noted in the direction of increased resistance to the drug, but not in that of increased sensitivity.

More recently Zischinsky²³ has reported his extensive experience on the use of morphine and related compounds in children. The only condition in which morphine was found to be contraindicated is the first stage of severe diphtheria, in which there is increased susceptibility to morphine. In subsequent stages of this disease morphine can be used even in the presence of cardiac involvement. This observer has found morphine particularly useful in this complication. In children with pneumonia or pleuritis associated with superficial respiration morphine is beneficial, and by increasing the depth of respiration it prevents atelectasis. Excitement following the use of morphine was observed in a number of instances. Morphine was not used by Zischinsky in infants under 5 months of age. The average subcutaneous doses recommended by him are as follows: In children between 5 and 6 months, 0.3 to 0.4 mg. ($\frac{1}{200}$ to $\frac{1}{150}$ grain); between 6 and 12 months, 0.4 to

0.5 mg. ($\frac{1}{30}$ to $\frac{1}{40}$ grain); 2 years, 0.75 mg. ($\frac{1}{80}$ grain); 3 years, 1 mg. ($\frac{1}{60}$ grain). Thereafter the amount administered should be about 2 to 3 mg. ($\frac{1}{30}$ to $\frac{1}{20}$ grain) less than the number of years until the dose for adults is attained. *Codeine* has not been found to be very useful. It should be given in larger amounts than usually advocated. The dosage recommended for babies of 6 months of age is 3 mg. ($\frac{1}{20}$ grain); for babies 1 year old, 5 mg. ($\frac{1}{12}$ grain); for small children, 10 mg. ($\frac{1}{6}$ grain); and for school children, 20 to 30 mg. ($\frac{1}{3}$ to $\frac{1}{2}$ grain). *Dicodid* (dihydrocodeinone) has been used mainly as a respiratory sedative in children in whom codeine failed to produce the desired effect. This writer observed no untoward reaction such as is described in adults. Nevertheless, he advised caution in the use of dicodid in children. The oral dosage recommended for use between the ages of 2 and 5 years is $\frac{1}{4}$ tablet of 5 mg. ($\frac{1}{8}$ grain); between 6 and 9 years $\frac{1}{2}$ tablet ($\frac{1}{4}$ grain); between 10 and 14 years 1 tablet ($\frac{1}{2}$ grain).

Another preparation, *acedicon* (acetyldimethyldihydrothebaine), was used in several hundred children. This is claimed to be the most reliable of all drugs in the treatment of cough. It has the advantage of being well tolerated from infancy on, and it is cheaper than morphine. In addition to suppressing cough it quiets the patient. It is particularly beneficial if the dyspnea and cough are painful. In whooping cough it is beneficial in some cases, while codeine usually is not effective. Habituation has not been observed. The dosage is more flexible than that of dicodid. The amount used for children is relatively higher than that for adults. The doses advised are: In infancy up to 2 years, $\frac{1}{4}$ tablet of 5 mg. ($\frac{1}{8}$ grain); from 3 to 7 years, $\frac{1}{2}$ tablet; and later, 1 tablet. He concludes that pediatricians are too cautious with the use of morphine in children.

The Use of Morphine in Patients with Heart Disease. Archambaud and Poulet² call attention to the diametrically opposite opinions expressed by clinicians regarding the indication or the contraindication of morphine in the presence of heart disease. These observers have used morphine extensively in cardiac patients without noting harmful effects. They claim that in cardiac patients with renal impairment it may reduce the volume of urine; in their opinion this is the sole contraindication.

The Effect of Morphine on the Gastro-intestinal Canal. Information concerning the effect of morphine on the normal gastro-intestinal canal of animals and of man and concerning its use in diseases of the alimentary tract is contradictory. The work of the earlier pharmacologists led by the contributions of Magnus indicated that morphine either produces no change or causes a relaxation of the small intestines. Probably because of these experimental findings morphine was thought to be contraindicated in conditions associated with intestinal distention, including peritonitis. More recently, however, Plant and Miller,¹⁵ Gruber and Robinson⁷ and Orr and Carlson¹⁴ have shown experimentally that both in animals and in normal man the characteristic effect is contraction resulting in increased tone and activity. Orr and Carlson observed that morphine sulphate in ordinary doses produced an increase in tone, in amplitude of segmentation movements and in frequency and amplitude of peristaltic movements. Large doses stopped peristalsis and decreased the tone, but had little effect on the segmen-

tation movements, which may be somewhat increased. The duration of effect of an average dose of morphine on the intestine was about 6 hours, both in animals and in man. A single dose of morphine caused retention of the barium meal in the animal and in the human stomach, increasing the emptying time to at least twice the normal time. A marked delay in the emptying of the ileum was also noted. The retarded progress of barium through the gastro-intestinal tract was attributed to a spastic effect exerted by morphine on the sphincters. Ochsner, Gage and Cutting¹² have studied the effect of morphine in dogs with experimental intestinal obstruction, and they also conclude that morphine stimulates rather than inhibits the activity of the small intestine. Abbott and Pendergrass¹ have attempted to clarify this problem. They claim that the two divergent views on the effect of morphine on the gastro-intestinal tract are the result of the use of two unrelated methods of study, one by roentgenologic investigation in man and in animals, the other by balloon technique in the surgically disarranged intestine of dogs and occasionally through fistulas in diseased human subjects. The results of their studies suggest that both views on the response of the small intestine to this drug are correct in part. On the basis of an experimental study in which intestinal intubation techniques, alone or combined with roentgenologic studies, were used in normal subjects, they conclude that the first effect on the small intestine of a single injection of morphine is stimulatory, producing a rise of tone which is greatest in the most reactive region of the gut, the duodenum, and slight or absent in the ileum. During this period the height of the contractions is diminished in proportion to the reduction in amplitude. About 20 minutes later a depressant action sets in and this may last for several hours, the tone falling. This secondary effect is also more marked in the duodenum than in the ileum. The general result of these changes is, first, to make the gradient of tone steeper, causing an initial rapid downward flow of duodenal and high jejunal contents toward the ileum. This produces a leveling off of the gradient and leads to a marked prolongation in the emptying time of the small intestine. These findings suggest that the effect of morphine is unfavorable in conditions associated with intestinal distention unless its advantages (analgesia and so forth) outweigh this aspect of its action. Abbott and Pendergrass nevertheless advise suspending final judgment until further information is available on the effect of repeated doses.

The Effect of Morphine on the Human Ureter. It is generally believed that morphine quiets and relaxes the ureter. Gruber⁶ studied the action of morphine on excised pig ureter, which was suspended in Tyrode's solution. He recorded both circular and longitudinal movements. He found that dilute solutions of morphine when applied to the pacemaker gave an *increase* in tone and in peristalsis, while more concentrated solutions gave a decrease in peristalsis but an increase of the pendular movements. Ockerblad and Carlson¹³ have made the bedside observations that from 2 to 5 minutes after the subcutaneous administration of $\frac{1}{4}$ grain of morphine to patients with colic due to ureteral stone the patients seemed often to be attacked by a severe paroxysm of pain, but in 15 minutes they were usually peaceful. These investigators therefore undertook the study of the effect of morphine on the normal human ureter in 50 patients with normal ureters. The peri-

staltic movements and changes in tone were registered on a kymograph with the aid of a catheter in the ureter. Doses of 10 mg. ($\frac{1}{6}$ grain), 15 mg. ($\frac{1}{4}$ grain) and 20 mg. ($\frac{1}{3}$ grain) increased the tone; the severity of increases depended on the size of the dose. The onset of the effect was from 2 to 5 minutes after injection. The rate of the ureteral contractions remained the same, but the tone and amplitude increased in *all cases*. In the upper segment of the ureter the morphine effect was less striking than in the lower segment. In one experiment the effect of morphine was studied for a period of 3 hours and was found to be still present at the end of that time. Atropine in doses of 0.6 mg. ($\frac{1}{100}$ grain) eradicated in from 8 to 12 minutes the changes due to morphine. Atropine itself does not abolish the normal contraction wave but may reduce its height. These observers also studied under the fluoroscope the effect of morphine on the kidney, pelvis and ureter, using both intravenous skioidan and retrograde injections of opaque media. Increased activity of the kidney, pelvis and ureter was noted after injection of morphine. A few observations have also been made on diseased ureters, but the response to morphine was not so regular or so great. The writers infer that after morphine in cases with ureteral stone the wall of the ureter tightens down on the stone and temporarily increases the pain. Some 15 to 20 minutes later, however, as a result of the cerebral and sedative effect the patient is relieved. This explanation is similar to that offered by Macht some 20 years ago.

These contributions indicate that significant progress has been made in recent years in the chemistry, pharmacology and therapeutics of the morphine group of alkaloids. It has been demonstrated that through proper alteration of the chemical structure changes can be brought about in the various biologic properties of morphine. *As yet, however, no substance in this group with effective sedative or analgesic qualities is known which is not, at least to some degree, associated with a tendency to habit formation and to addiction.*

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RADIOLOGY

UNDER THE CHARGE OF

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DISEASES OF THE LUNG.

THE roentgenographic portrayal of the pathologic reactions within the anatomic units of the lung is dependent on certain factors: (1) Without air there is no differentiation of tissue. This is especially exemplified in the newborn infant's chest where no air has entered the lungs. The lungs cast the same shadow on the film as any other unaërated tissue of the body. (2) Any increase or decrease of the air content of the anatomic units, if of sufficient amount, can be portrayed on the film. The air within these units surrounds the larger and denser structures of the lungs and brings them into relief. (3) Any structural change which increases or decreases the air content of the air sacs and bronchioles will be portrayed on the film, either by its decreased density or its increased density, provided it is surrounded by other air sacs which are well aërated. Most of the structural changes show an increased density, as bronchopneumonia, but there are a few structural changes which show a decreased density, as bronchiectasis or localized emphysema. (4) In the healthy lung only the larger structures, such as the arteries and bronchi, are seen on the film. The structures of the air sacs, terminal bronchioles, the smaller arteries and their capillaries, and the veins are too delicate to cast any shadows. Furthermore, the air content of these anatomic units tends to blot out some of the larger bronchi, arteries and lymphatic structures, as they approach the anatomic units.

With this introduction, Wasson proceeded to discuss the pathologic reactions within the anatomic units. Pathologic reactions within the anatomic units can take place in the bronchioles and their air sacs, the arteries, veins and their capillaries, the lymphatic system or the supporting connective tissue framework for these structures. In a lesion of sufficient size to be seen on the roentgenogram, all of these anatomic structures are most certainly involved. In the usual clinical case with inflammatory reactions an involvement of one or more secondary lobules is necessary for roentgenographic portrayal or to produce clinical symptoms. Miller estimated that there are from 50 to 250 anatomic units in a secondary lobule and that a secondary lobule measures from 1.5 to 2.5 cm. in diameter. Bronchiectasis and emphysema both produce dilatation of the air sacs and of the bronchial lumen but differ entirely in their pathologic appearance and their pathogenesis. Likewise, atelectasis, cellular exudate and edema will obliterate the air spaces and cast the same roentgenographic shadow but have an entirely different pathologic appearance and origin. The differentiation by the roentgenologist between these processes within a small group of

anatomic units would be impossible if only the small localized lesion were considered. Few of the pathologic processes taking place within the vascular system of the anatomic units can be differentiated from certain pathologic reactions in the bronchioles and air sacs, where the air content is completely obliterated, if only a small group of anatomic units is considered and if no consideration is given to the structural changes in the rest of the chest. The lymph channels may become distended or they may be compressed by adjacent disease. The walls of the lymphatic channels may be caught in the pathologic process and destroyed or in the more chronic conditions the walls may be thickened with definite fibrosis. The flow of the lymph may be blocked by cells or debris. Nodes of lymphoid tissue are not plentiful within the anatomic units but those present may have acute inflammatory reactions or chronic fibrotic reactions. When such pathologic reactions within the lymphatic system of the anatomic units reach sufficient proportions as to interfere with the air content of the adjacent air sacs and when a sufficient number of units are involved, the reactions may be portrayed on the roentgenogram. The reactions within the connective tissue framework supporting the bronchioles and their air sacs, the arteries, veins and their capillaries, and the lymphatic system may undergo either acute inflammatory changes or chronic fibrosis.

An attempt should always be made to divide the pathologic reactions within the anatomic units into those involving the ventilating system, those involving the vascular system and those involving the lymphatic system. For differentiation the roentgenologist must turn to the structural changes in other portions of the lungs, the mediastinum and its structure, or the chest wall. The differential diagnosis is most frequently made by a study of the structural changes in the rest of the bronchial system when the bronchioles and air sacs are involved. In diseases of the vascular system with stasis of flow in the capillaries, the differential diagnosis is made by a study of the heart and great vessels, the location of the shadows and the anatomic appearance of the rest of the chest. Diseases primarily of the lymphatic system are differentiated by a study of the reactions within the lymph nodes along the major arteries and bronchi, or of those nodes at the lung roots or in the mediastinum.

This dissertation constitutes an interesting prelude to a study of the roentgenographic diagnosis of lesions of the lung, particularly so when it is coupled with the report of Barclay and others on roentgenographic studies of the excretion of dusts from the lungs. Barclay and his co-workers insufflated radiopaque dusts into the lungs of animals in order to study the manner and rate of elimination of these dusts from the healthy respiratory tract. From their own experience and what they could learn of that of others, they could affirm that the most important mechanism is that provided by the cilia and the secretion of mucus, for it extends over most of the respiratory tract and is the only known means of clearing substances from this large area other than the pathologic or psychopathologic act of coughing. The ciliated epithelium is distributed throughout the trachea and bronchi down to the very fine bronchioles (0.2 mm. in diameter). Interspersed among the ciliated cells in tubes of this size are non-ciliated cells; in the larger tubes the ciliated cells are continuous and even line the openings of the

ducts. A mucous blanket forms a continuous layer over the ciliated epithelium and is carried upward, with the foreign bodies which are deposited on it, by the ciliary action. Much depends on this mucous blanket, for the ciliary action is rendered ineffective if it is either too scanty or too profuse, too dilute or too concentrated. A tendency for mucus to move spirally upward had already been noted in former communications, also the peculiar direction of movement at the areas of junction of the bronchi. India ink, injected subpleurally into the lung of a decerebrate cat, took only 14 minutes to reach the distal end of the tracheal cannula, that is, to travel about 4 cm. within the lung and 8 cm. up the trachea. The rate of movement is considerably greater in the trachea than it is in the lung; a particle of fine starch powder may be carried along in the opened trachea of the cat as fast as 3.5 cm. per minute. Cilia are not present on the vocal cords and anterior commissure of the larynx but are present on the posterior commissure. Hence, all mucus must pass up by the posterior commissure, a fact which partly explains why tuberculous lesions of the larynx are commonest in that region.

Inflammatory conditions may destroy ciliated epithelium and it may not be regenerated; in such cases the mechanism of cough has to be brought into play. Hence, any area that has been the scene of an inflammatory process may be vulnerable, for it may have lost the main weapon for combating and getting rid of foreign matter. Even in the worst cases of pneumoconiosis, it was reported, ciliated epithelium is usually retained to the end, despite the presence of pus in the bronchioles. Coughing is not usually resorted to by healthy persons even in a dusty atmosphere but, in the presence of irritant fumes or smoke, it is the normal response to irritation of the mucous membrane. The mechanisms of excretion from the alveoli are not yet fully understood. Wandering phagocytic cells undoubtedly play an important part, particularly in the case of long standing exposure to dust, but it is possible that other factors, for example, the variation in volume of the alveoli with the phases of respiration, may come into the question.

The part played by the smooth muscle of the bronchi and perhaps of the trachea in the process of excretion still needs further study. The muscles are distributed in a "geodesic network" that must have a functional significance. The tubes increase in muscularity as they decrease in caliber. In studies of the physiologic actions of the smooth muscle there is a conflict of opinion, which is in part due to the technical difficulties imposed by the rapid alternation of inspiration and expiration. Healthy lungs should have no difficulty in coping with the minute amounts of dust that are inhaled even in the most dusty atmospheres, provided the subject is given an adequate rest period away from these atmospheres. Experiments with acetic acid solution introduced after dust insufflation, with the introduction of dust in dilute syrup and of dust in saline solution, showed that the lungs have no mechanism to prevent such solutions from reaching the alveoli. Under such circumstances excretion is much prolonged and massive collapse of the lung may result. In one of the animals studied by Barclay and others the pathologic process continued steadily once it had begun, though the initiating agent was in large measure excreted long before the animal was killed. There was some histologic evidence that cells were removing

the dust and passing from the alveoli up the lymphatics but Barclay and his associates never saw any roentgenologic evidence of lymph gland involvement.

In discussing the roentgenologic recognition of certain bronchomycoses involving occupational risks, Fawcett paid particular attention to roentgenologic appearances found in the chests of agricultural workers following the inhalation of moldy dust of hay or grain. The incidence of this disease is seasonal and definitely depends on a moldy condition of hay or grain after a wet season. The condition sometimes is associated with grain and usually coincides with threshing time. The condition may appear as an epidemic. Practically all the patients are found among agricultural laborers and stable workers. The outstanding symptom is dyspnea. It is so marked that no other symptom seems of any importance. The first diagnosis is almost invariably tuberculosis; but when repeated examination of the sputum is negative for tubercle bacilli, yet constantly shows the presence of microfungi, one cannot help suspecting the latter as the causal agent. Their pathogenicity is extremely difficult to prove but the clinical picture and the response to treatment are striking.

Prompt diagnosis is important because the condition is curable in its early stages by potassium iodide therapy and autogenous vaccine; but may become incurable later, progressing to the dense fibrotic stage, or that of calcareous nodulation. Or it may provide a soil for the growth of more serious disease by interfering with ciliary action and allowing malignant tumor or such slow growing organisms as the tubercle bacillus to get a foothold. The history and symptoms vary according to the causative fungus.

Roentgenologic indications are scanty but important. The lung markings are more defined than normal, in that the fine reticulation and shadows of peribronchial vessels are more evident, resembling a lymphangitis. In the second stage there may be a rather soft snowflake mottling, widely distributed throughout both lungs; it lacks the peripheral distribution and the sharp definition and density of the typical silicotic nodule and resembles the indefinite changes of bronchitis rather than a miliary tuberculosis. There is a tendency for the midlung fields and bases to be affected more than the apexes. In the third stage there is a gradual increase in the density of the mottling, particularly toward the bases. The occurrence of coalescent areas of fibrosis marks progression into the fourth stage, with marked restriction of the diaphragmatic movements and a recurrence of emphysematous areas, and the linear markings are much exaggerated.

Fawcett distinguished the mycosis of hay workers, in which sometimes the sputum smells like brewers' yeast, the mycosis of grain workers, the mycosis of soil workers, a type characterized by mixed infection in which *Botrytis cinerea* (a fungus associated with butter, milk and decaying vegetation) predominates, and the mycosis in hematite iron-ore workers (all showing a type of fungus found in rotting timber).

Clinical results suggest that fungi play a part in dust diseases and that bronchomycosis may play some part in the vexed and vital problem of silicosis, whether by collapse of the alveoli caused by occlusion of the bronchioles, by interfering with the expulsive action of the cilia or by sensitizing the lung; when fungi invade the lung they break down its

defenses against the mechanical injury by the particles and the biochemical action of the silica. It may be that there is a biologic as well as a biochemical and mechanical factor in the chain of events which leads to the condition we call silicosis. It is believed that the presence of dust-borne microfungi involves an occupational risk.

In a symposium conducted at the twentieth annual meeting of the Radiological Society of North America the subject of silicosis was discussed. Sayers and Jones credited Collis with the most comprehensive historical review of the subject of industrial pneumoconioses. The pneumoconiosis characterized by nodular fibrosis has to date been shown clinically and experimentally to be associated only with the inhalation of dusts containing silica. Moreover, it has been established beyond doubt that exposure to dusts consisting wholly of free silica (quartz) produces this disease, which has not been shown to be the case for any other specific dust. Of free silicas which occur in Nature, that known as quartz is by far the most common. This form of free silica exists in two polymorphous forms, low and high quartz; distinction between the two classes is of little importance. The next most common form in which free silica occurs in Nature is the amorphous hydrated form known as opal ($\text{SiO}_2\text{-H}_2\text{O}$), a silica of colloidal origin which occurs abundantly in the diatomaceous earths, less resistant to reagents than quartz. Another type of free silica frequently found is flint, and with flint is found chalcedony, a waxy translucent form of silica interpreted as consisting of fibers of quartz with a small amount of interstitial opal. Other forms of free silica occurring less abundantly in Nature are tridymite, cristobalite, and siliceous glass or vitreous silica.

Sayers and Jones charted the great variety of uses to which silica is put in industry and the kind of silica adapted to each purpose. A recent survey revealed that about 9% of the industrial workers are employed in occupations in which the silica hazard requires consideration; nearly 1,200,000 individuals are potentially exposed to a silicosis hazard in the manufacturing and mechanical industries alone.

In experimental work, only the silica-containing dusts have uniformly produced a proliferative reaction. The particle size of the atmospheric dust bears a definite relationship to the injurious effect produced. The silica must be present in the air in particles small enough to enter the finer air spaces and of such dimensions that phagocytes may engulf them. The natural defenses of the respiratory tract probably prevent many particles larger than 10 microns from ever reaching the finer divisions of the lung and such as do are likely to be expelled with the bronchial secretions. The soluble silica plays a definite part in the production of the disease and the size of the particle also affects the rate of solution, owing to the fact that the smaller the particles the greater the total surface area exposed to the action of the solvents. The size distribution of various industrial dusts was presented in chart form. Most of the particles found on microscopic examination of the lung fall within the limits of from 1 to 3 microns. The harmfulness of a given dust containing free silica is directly influenced by the number of particles it contains of free silica less than 10 microns in diameter and probably the greatest harm is produced by those between 1 and 3 microns.

Some authors have expressed the opinion that the presence of other inorganic dusts in the silica-containing atmosphere may tend to influence the effects of the silica inhaled. The relative absence of silicosis in the cement industry was thought to be due to the calcium present. Investigations have led to the belief that the absence of evidence of extensive pulmonary fibrosis is due to the fact that there is insufficient total exposure to free silica (considering concentration of dust and duration of exposure) rather than that there is any neutralizing effect due to the calcium.

In the cases of so-called acute silicosis, resulting from the inhalation of air containing high concentrations of silica along with strong alkali in a finely powdered form, there is need of scientific research to determine the actions of such concentrations of silica alone, as well as the reaction resulting from the inhalation of the alkali in the absence of silica, before the whole truth in regard to these cases will be known.

It is important to secure a complete occupational history and try to fit the dust exposure while at such work into the picture found representing clinically and radiographically that of advanced silicosis. By recording complete data one is able to express the average exposure in terms that may be compared to other cases of similar severity.

The question of predisposing factors relating to the cause of silicosis has been given as much attention as the exciting cause. It has not been scientifically proved that race itself exerts any influence on either the production or the retardation of pulmonary fibrosis due to silica. Climate, temperature and related factors may safely be assumed to play no important part in the production of silicosis. It is obvious that sex can play no part in a disease of this nature except that the type of industry wherein the silica hazard is found employs relatively few women. The relationship of age *per se* has not been demonstrated to be of great importance. Respiratory infection has been shown to be the greatest predisposing and complicating factor in the development of silicosis. It is essential for the individual to possess excellent functioning nasal passageways, in order that the self-cleansing mechanism may work efficiently. Chronic bronchial asthma was considered a predisposing factor affecting individual susceptibility. Chronic infections of a local or constitutional nature may be shown to influence materially the incidence of silicosis. Preventive measures should be taken to control such infections in the sinuses and dental regions as may serve as a source of organisms resulting in the occurrence of bronchospirochetosis. Acute pneumonic conditions as well as the more chronic lung changes, such as chronic bronchitis, bronchiectasis and bronchiolectasis, emphysema, and pleurisy, all tend to decrease the ability of the lung to rid itself of foreign materials through lessened lymphatic drainage and decreased power to force the bronchial secretions and foreign matter from the lungs. The dilated bronchi and areas of emphysema developing in persons as a result of abnormal demands made on the lungs by glass-blowers, divers, professional singers, trumpeters and the like, seldom advance to the point at which the individual offers any complaint until infection has entered the picture. The lung changes accompanying silicosis might be expected to lead to conditions favoring bacterial invasion. The increased incidence of tuberculosis among occupational groups exposed to silica has been clearly shown in every instance in

which this hazard exists. The initial studies of silicosis by workers in South Africa were started by a demand made on the health authorities to determine the cause of the excessive mortality from tuberculosis, which was increasing at a rapid rate among the gold miners there. The statement of Gardner that "At least 75% of those human beings who develop silicosis die of tuberculosis, which may make its appearance at any stage of the disease" stresses the importance of the problem of silicosis from the viewpoint of activities against tuberculosis. It has been shown that the tubercle bacillus will grow more rapidly on culture media to which a small amount of silica offers a favorable medium for the growth of the organism and that animals exposed to silica, when inoculated with a strain of tubercle bacilli of low virulence, will develop systemic tuberculosis and die, while control animals not so exposed usually are not seriously affected by injections of such organisms. It is not so much what the condition of the silicotic is today as what it will become tomorrow. The tendency of the fibrosis to progress, even after the patient has been removed from exposure, was stressed. No remedy has been shown to be of value in elimination of the pulmonary fibrosis, although certain improvement in symptoms may be noted after the victim is removed from exposure.

Simple silicosis not complicated by tuberculosis or other infections should be roentgenologically diagnosed reasonably early and with accuracy, according to Ernst. The practical roentgenologist realizes that there are certain essential technical requirements in order that the correct interpretation of roentgenograms may be possible. The ideal roentgenographic examination projects the normal and abnormal thoracic densities on a film true to size, shape and outline, and devoid of movement or pulsations of the minute lung structures themselves. The potential current employed or strength of the Roentgen ray beam is likewise important and should be accurately calculated for each chest examined. The patient should be carefully measured in centimeters and the probable penetration of the chest thus estimated in terms of the number of kilovolts to be employed. The size of the focal spot of the Roentgen ray tube is another important consideration, likewise the distance of the tube from the film and the patient. The time factor should remain uniform and preferably less than a twentieth of a second. Uniform reduplication of exposures over a period of many years is a most important requirement in serial lung examinations.

Lanza stated that silicosis is essentially a chronic, progressive disease. One advantage is that one can watch the progress of the disease by serial roentgenographic examinations. As a result of intensive occupational studies, where workmen were kept under observation over a period of years from the time of entrance into the industry it was possible to measure with a fair degree of accuracy the length of exposure necessary to produce definite silicosis, demonstrable by roentgenographic examination under a given, constant set of conditions. In the old days of dry drilling in the mines, 5 years' continuous exposure, as a rule, produced definite clinical silicosis with appreciable disability; after tubercle infection was demonstrated, death usually resulted in not longer than two years. In Lanza's series those who developed silicosis were dead, on the average, 10 years after commencing work in the mines. Recent examinations elicited definite cases of silicosis among

employees after 20, 30, 40 or even more years in the same foundry. Obviously, the underlying cause of these variations in the intensity of silicosis was the dosage of silica which the individual received. Actually, in industrial practice they found numerous variations in these factors. Variations among those exposed to an identical hazard result from abnormalities in the individual, chief among which are preëxistent pulmonary disease and syphilis. Experience indicates that persons with a 4 plus Wassermann reaction contract silicosis in about half the time of normal persons. The principal and distinctive symptom of silicosis is dyspnea; even in cases in which the exposure is severe, dyspnea comes on insidiously with a gradually increasing short wind and a corresponding decrease in working ability, an increased tendency to catch cold and an irritative, unproductive cough. The condition may progress to total disability from dyspnea. Usually before that point is reached, especially if the exposure to silica has been severe, a tuberculous infection occurs, with sudden loss of weight, fever, night sweats, copious expectoration, rapid loss of strength, and death within a few months. In others, the tuberculous infection progresses slowly and only roentgenographic examination will reveal the structural damage to the pulmonary tissue. The general experience is that, barring accidents, the victims nearly always die of tuberculosis, and the more intense the exposure to silica, the sooner does tuberculosis result and the more rapidly does it progress. Even when the silica dust hazard is comparatively mild, the mortality from tuberculosis is above the average.

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THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

DECEMBER, 1938

ORIGINAL ARTICLES.

A GLOMERULAR DOMINANCE IN BRIGHT'S DISEASE.*

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To Richard Bright in 1827 and in subsequent publications the disease that we now know by his name was very simple. His clinical conception was unified about one characteristic, boiling the urine caused a precipitation; this meant disease of the kidney; albuminuria was evidence of a pathological state of the kidney. Bright recognized that with albuminuria went varying manifestations of abnormal function, not of the kidney alone, but of the body in general; on postmortem examination he saw that the kidneys from these patients varied greatly in appearance, but there was unity in the fact that none of the kidneys were normal. To Richard Bright albuminuria was the dominant characteristic of kidney disease during life, and on postmortem examination disease of the kidney was for Richard Bright the dominant characteristic. Whatever variety there might be in the clinical picture, and Bright recognized and described many of them, the common feature was albuminuria; whatever variety there might be in the pathology of the kidney and other organs, and Bright described and pictured most of these as we recognize them today, the common feature was that the kidneys were diseased. To Richard Bright the concept of kidney disease was simple; neither in 1827 nor in 1836 did he use the term, nephritis. Had he done so, very probably he would have used the terms, *nosos nephritis*, in the original Greek usage "disease

* The Gordon Wilson Lecture of the American Clinical and Climatological Association, read at a meeting of that society held at Atlantic City, N. J., on May 2, 1938.

in, about or concerning the kidney", that being the significance in classical Greek of the ending "-itis" after the name of an organ or tissue as indicated by Thucydides having Nicias say "nosos nephritis", while Hippocrates in one place uses the words "phthisis nephritis". It was only at a later date that the ending "-itis" came to have the medical connotation of "inflammation of", and this departure from the original usage has put us in a dilemma of terminology that long has been a bug-bear to classificationists of kidney disease.

The pathologists early found that under the microscope there was fully as much, if not even more, variation in the findings in different patients, who during life had shown albuminuria as evidence of disease of the kidney, than was apparent in the different gross appearances of the kidney as seen and pictured by Richard Bright. For a time pathologists maintained a unity of concept in that they considered these variations in both macroscopic and microscopic appearance of the kidneys no more than an expression of the patients having died at different stages of a single type of kidney process. This was the view in the time of Frerichs, 1851, and continued to be accepted by some until Weigert, in 1879, crystallized the idea that had been steadily growing in favor in England and Germany, that not one, but several, disease processes were present in nephritis or Bright's disease, the concept which now prevails among both pathologists and clinicians.

This latter point of view has been responsible fundamentally for complex classifications of Bright's disease. This complexity has increased as the microscope and clinical methods have shown more and more variation in individual patients to be used as a basis of grouping them in accordance with their resemblances and differences into more and more groups, each regarded as possessing some important individual characteristics, until classifications, whether of the pathologist or of the clinician, have grown into the great complexity, such as now very generally prevails.

A long time interest in Bright's disease, both in its pathological and clinical manifestations, has made me wonder whether such complexity of classification is necessary to a satisfactory understanding of the disease, and whether there may not be more to gain in an understanding of what happens when the kidney becomes diseased, by considering more the common factors and functions among the disturbances and less the differences that multiply the subdivisions of our classifications.

It is true that the normal kidney is very complex both in structure and function, and yet, after all, it is only an aggregate of units, supported in a framework of tissue functioning only to hold these units together and to protect them from external injury. This unit centers itself very naturally in one structure, the glomerulus, into which comes a blood flow and out of which passes a blood flow and a canal lined by cells with a definite function. Here is a unit

of concept in renal function, normal and abnormal, the glomerulus. Is it possible to build on such a unitary concept a simpler understanding of the diseases of the kidney?

The glomerulus is a vascular unit, an aggregation of branching and converging capillaries, covered by a layer of greatly thinned, tubular epithelium connected with a tubule lined at different levels by various types of cells. The total surface of the capillary tuft in the glomerulus is great, and in their aggregate an enormous area of capillary surface exists in this way. Through the glomeruli daily passes a vast amount of blood, aerated and loaded with many substances collected from all parts of the body. Between this circulating blood within the glomerular tuft and the external world, communicated with through the tubule, ureter, bladder and urethra, exists but a thin membrane of dual composition, capillary wall and renal epithelium. The situation is, in a way, analogous to that in the lung, where capillaries are spread out in the walls of the pulmonary alveoli, so that in the lung between the circulating blood and the external world is but a thin membrane made up of capillary wall and pulmonary epithelium. In each, endothelial and epithelial structures are in close apposition to form a colloidal membrane, but these two membranes, so alike in structure, function in vastly different ways; in the kidney, the normal membrane allows the passage of water and certain small molecule solutes; in the lung, the normal membrane allows the two-way passage of two gases, oxygen and carbon dioxide; each of these membranes holds back what the other normally allows to pass; this illustrates how differently structures, which under the microscope look alike, may function and emphasizes the probability that structures may undergo changes, that profoundly alter their function, without our being able to see any structural change in them under the microscope.

The afferent blood supply to the glomerulus serves to bring to the glomerulus blood for it to lose certain constituents, which pass through the glomerular membrane into the tubule. The efferent blood supply carries this blood to the tubule, where through the epithelium of the tubules and its basal membrane further changes in the blood are made, largely additive in nature. The tubule serves to carry off the water and its solutes that pass through the glomerular membrane but in this passage modify this fluid, largely by a subtractive process, before it is discharged into the external world as urine. What happens in this way constitutes the function of the kidney, a function dominated by the glomerulus of each unit, a function that is in essentials a physico-chemical process, in which the glomerular membrane plays the dominant part. For this mechanism to function normally there is necessary a free blood flow through the glomerulus and a normal glomerular membrane; these are dominantly important. Of subsidiary importance is a normal epithelial lining to the tubule running from the glomerulus.

If the glomerulus dominates the kidney in its normal function, as just described, so the glomerulus dominates the abnormal function that occurs in Bright's disease or, in other words, there is a glomerular dominance in Bright's disease. Let me explore this idea further. As already stated, for normal renal function there is necessary to each unit of structure a free blood flow to the glomerulus and a normal glomerular membrane discharging into a normal tubule; in this, glomerulus is dominant and tubule subsidiary in function. With these functioning normally in a normal body we have urine, proportionate in amount and specific gravity to intake of fluid and free of albumin, casts and cells, a blood stream with its constituents balanced within relatively slightly fluctuating figures and a blood pressure within normal limits. In Bright's disease some or all of these in varying proportions depart from their norms, and these departures along with secondary effects on body organs and tissues make up the clinical picture of the various forms of Bright's disease.

In Bright's disease the glomerular membrane either leaks or holds back constituents of the blood stream, and the blood flow through the glomerulus remains normal or is throttled down to a lessened flow; the throttling may take place inside or outside of the glomerulus. Acceleration of blood flow through the glomerulus occurs; as far as Bright's disease is concerned, this seems to be only a compensatory action and merely helps to lessen the effect of retarded function in other glomeruli. Finer glomerular leakage permits molecules larger than normal to pass, such as albumin, globulin and fibrinogen, and holds back cells; coarser glomerular leakage permits in addition the passage of cells, red blood cells and white blood cells. A thickened glomerular membrane plays a part in retention of substances otherwise excreted from the blood stream, but retention chiefly is a function of throttled blood flow, whether the throttling is outside the glomerulus or due to narrowing of the capillary lumen inside the glomerulus. Retention also is related to the atrophy and disappearance of glomeruli, which occurs in Bright's disease.

In Bright's disease there are lesions in the tubules, but these changes are relatively unimportant in most cases so far as the clinical picture and renal function are concerned. Their part definitely, so far as we know at present, is a subsidiary one.

If the glomerular changes dominate in Bright's disease, as seems to be the case, then we can unify our concept of Bright's disease, building around glomerular function. The sequences of pathological changes in the glomeruli largely can be simplified to those causing glomerular leakage and those causing glomerular throttling in varying combinations of severity.

If the glomeruli leak, we have albuminuria with cylindruria or hematuria; leukocytes, too, appear, but rarely are they very numerous in the urine of simple Bright's disease. If leakage of albumin continues so that plasma protein becomes low, we have chronic

renal edema of the body. If the glomerulus only leaks, there is no abnormal retentions in the blood stream and no elevation of blood pressure. If the glomeruli are throttled, we have abnormal retentions in the blood stream and elevation of blood pressure. If there are abnormal retentions in the blood stream, and this chiefly is non-protein nitrogen retention, anemia and uremic symptoms develop. If the blood pressure is elevated and continues high, we have secondary cardiovascular changes. If these are sufficient to cause cardiac decompensation, circulatory edema will appear. These several changes develop in different patients with Bright's disease in different proportions; from this is derived the varying symptomatology and physical findings in what we call Bright's disease.

As far as throttling of the glomerular blood flow is concerned, the effect is the same whether the throttling is in the capillaries of the glomerulus, in the afferent or even efferent arteriole of the glomerulus or in the larger renal vessels anywhere in their course between the aorta and the afferent arteriole of the glomerulus; not the situation of the throttling, but its degree, is what determines the effect on function. This is well shown by the experimental work of D. R. Drury, published in April, 1932, who, placing a not-binding ligature about the renal artery of young animals, got his throttling effect from the artery gradually becoming constricted, by the pressure of a ligature that had not stretched as the artery grew larger with growth of the animal, this producing renal atrophy with polyuria and nitrogen retention; and of Goldblatt, in which the throttling of the glomeruli was brought about by a constricting band applied about the main renal artery of adult animals, resulting in a steady rise in blood pressure without or with disturbance of renal function, depending upon the degree of constriction of the main renal artery, work first reported by Goldblatt on November 11, 1932, before the Academy of Medicine of Cleveland and subsequently published in 1934. It is of further interest that in 1909 William S. Halsted published a paper entitled "Partial, Progressive and Complete Occlusion of the Aorta and Other Large Arteries in the Dog by Means of the Metal Band" in which he has an illustration of the kidneys, on the artery to one of which had been placed a compressing metal band; that kidney is atrophied to about one-quarter the size of the one on whose artery no band had been placed.

In the preceding paragraphs I have attempted to build up a concept of Bright's disease unified about the glomerulus, a glomerular dominance in the process. To bring about the clinical picture and physical findings of Bright's disease two changes in the glomeruli are of dominant import, glomerular leakage and glomerular throttling. If you will accept these ideas, let me elaborate them in relation to the classification and the symptomatology, including physical findings, of Bright's disease, showing how from these glomerular

changes, leakage and throttling, can come about the chief clinical findings that we encounter in Bright's disease.

First, as to classification, for a long time I have taught to my students a very simple clinical classification of Bright's disease as follows:

Acute and Subacute Bright's Disease (Hemorrhagic, Edematous).

Chronic Bright's Disease With Renal Edema.

Chronic Bright's Disease Without Renal Edema.

In these groups glomerular leakage dominates in all except the last; in the last glomerular throttling dominates. With dominant glomerular throttling there is practically always an accompanying, but less important, glomerular leakage; with dominant glomerular leakage there may be periods of glomerular throttling. In certain patients the two processes seem of almost equal importance; these may be called Mixed Types of Chronic Bright's Disease.

What I have given is a clinical classification. At different stages there is a corresponding pathological picture. For example, the first three chief groups would be called by the pathologist glomerulonephritis, acute, subacute and chronic; in them, glomerular leakage has been the chief disturbance of function; the finer histological changes in the glomeruli probably would be quite different from case to case at any of the three stages, acute, subacute and chronic, depending on what part or parts of the glomerular structure was involved, on how great a degree of involvement there was and on how long the process had been going on, whether the leakage is chiefly of albumin or of blood cells. These changes would range from those so slight as to be detected only with special staining technique, which occur when there is a very extensive leakage of albumin as in the edematous type of acute Bright's disease (nephrosis syndrome) to those marked enough to make the glomeruli visible to the unaided eye as in some cases of subacute and chronic Bright's disease. Sometimes, but not always, these different pathological appearances can be recognized by the clinical course of the disease; to attempt to do so in individual cases would bring too great uncertainty to justify the introduction into the clinical classification of numerous subdivisions to tally with these pathological variations.

In contrast to these three, the last group, Chronic Bright's Disease Without Renal Edema, with a definite distinctive clinical picture is made up of cases that pathologically show great variation. The reason for this is that throttling of the glomeruli dominates and that is the chief cause of the most important clinical characteristics of the group, namely hypertension, nitrogen retention and anemia. The result is much the same whether the throttling occurs inside the glomerulus, just outside in the glomerular arteriole or more distantly in the course of the renal artery and its branches. This throttling can be the end result of 4 different types of pathological change in the kidney: 1, glomerulonephritis; 2, vascular nephritis,

sometimes called malignant hypertension; 3, pyelonephritis; 4, rarely, so-called nephrosis. Nephrosis in my opinion, is a form of glomerulonephritis, in which glomerular leakage of albumin is the outstanding clinical manifestation.

You can follow in certain instances a patient that progressively will pass through stages showing the clinical features of all four main groups in the above clinical classification, that is acute, subacute and chronic Bright's disease with renal edema and finally, chronic Bright's disease without renal edema; this not infrequently happens. In the beginning glomerular leakage dominates; at the end glomerular throttling dominates; in between, both processes go on in varying proportion. As throttling of the glomerulus becomes prominent, leakage lessens; hence with a marked early albuminuria blood pressure is normal, and there is no nitrogen retention and no anemia; later as albuminuria lessens, blood pressure rises, nitrogen retention begins and later, anemia follows. As these changes go on, glomeruli, at first larger than normal, shrink, tubules atrophy and interstitial tissue increases; the early large kidney of acute and subacute glomerulonephritis becomes the secondarily contracted kidney of chronic glomerulonephritis. Other patients commencing as acute hemorrhagic Bright's disease eventually will reach this same end stage, unless they die at an earlier stage or recover from the acute stage.

By no means is it possible in all cases to trace clinically these several stages. Some cases recover in the acute stage, and there is no subsequent progression. There may be a long latent period of apparent health between the early acute and the late chronic atrophic stage; the acute stage may have shown no symptoms; possibly from the onset the process has been insidious, free of symptoms and so clinically latent, until glomerular throttling begins; prior to this, the stage of glomerular leakage has been so mild as to pass unnoted.

In just this same way essential vascular hypertension eventually leads to glomerular throttling; when it does, the clinical picture is the same as that of the late stage of glomerulonephritis as just described. This change may be slow or rapid in its progressive development, and this causes different clinical pictures. When rapid, some like to use the term, malignant hypertension. To me it has seemed less confusing, if the term malignant hypertension is not used, since I consider it but a variant of vascular nephritis and not a distinctive pathological change. Sometimes evidence of vascular lesion with hypertension appears only at the time that glomerular throttling is causing its usual characteristic renal symptoms; at other times, it long antedates evidence of disturbed renal function, and we have almost only hypertension as an evidence of glomerular throttling. Pathologically this is vascular nephritis.

Similarly, pyelonephritis may develop into a chronic or even healed stage, so far as the infection is concerned, but one in which

kidney atrophy with glomerular throttling develops to end in a clinical syndrome having the chief characteristics just described for the late stages of chronic glomerulonephritis or of vascular nephritis, namely, hypertension, renal retention and anemia. Pathologically, both glomerular lesions and vascular lesions in combination contribute to this end result in which atrophy and connective tissue increase are prominent.

Particularly interesting in this respect is a rare case of so-called nephrosis, which ends in a stage of high blood pressure, nitrogen retention and anemia. The change that takes place is almost a pure demonstration of what I have been discussing, namely glomerular dominance, at first with pure leakage and later with throttling. The glomerular lesion of so-called nephrosis is very simple; the glomerular membrane is changed, so that it no longer holds back albumin and globulin, but few or no cells go through. The only histological evidence of this is a slight hyaline appearance and a very slight thickening of the capillary wall and opposed epithelial membrane; special staining technique is required to demonstrate these slight changes. If the condition retains its nephrosis characteristics, as time goes on, the only change is more thickening of the glomerular loops but without cellular proliferation; only glomerular leakage goes on. In a very rare instance, however, the thickening of the wall gets marked enough to lead to some obstruction of blood flow in the capillary loops, *i. e.*, throttling of the glomerulus; now blood pressure rises and nitrogen retention begins; the late stage here is just as described for the preceding three forms; throttling of the glomerulus eventually has dominated the picture. George Fahr has described such cases; I have never observed one.

In acute nephritis, in which glomerular leakage dominates, occasionally temporary throttling of the glomeruli appears, and in these cases of acute nephritis hypertension and nitrogen retention appear for a short period, later to disappear.

Throughout this discussion I have used the term renal edema to mean that form of edema resulting from low plasma protein, especially low plasma albumin; it has no relation to circulatory insufficiency. With glomerular throttling we have hypertension; if hypertension is marked enough and persistent enough, cardiac hypertrophy results, and this often leads to cardiac insufficiency and the edema of congestive heart failure, or circulatory edema. These two types of edema should be distinguished in an understanding of Bright's disease.

With patients of this last group, Chronic Bright's Disease Without Renal Edema, seen only in the late stages, it may not be possible to say what type of lesion of the kidney is responsible for the condition. When there has been opportunity to follow the clinical developments over a period of time, as a rule, some one of these four separate ways of progression into the end stage can be recognized

as having led up to the end stage of Chronic Bright's Disease Without Renal Edema, and we are able to say that glomerular throttling has resulted from progressing glomerulonephritis, vascular nephritis, pyelonephritis or the nephrosis syndrome.

Summary. In the preceding discussion I have attempted to elaborate a concept of Bright's disease in which the explanation of its major clinical symptoms and signs can be found in disturbances in the integrity of the function of the glomeruli of the kidney. These disturbances in glomerular function are: 1, abnormal leakage of blood constituents into the tubules of the kidney; and, 2, throttling of the blood flow through glomerular capillaries. These occur in varying combination of intensity from the one in which leakage is almost the sole abnormality to the one in which throttling of blood flow is the chief departure from normal with all sorts of combinations of these two disturbances in different individual patients. The most distressing clinical result of leakage is renal edema and of throttling is hypertension and nitrogenous retention. It is this that I have meant by "A Glomerular Dominance in Bright's Disease."

HEMOLYSINS AS THE CAUSE OF CLINICAL AND EXPERIMENTAL HEMOLYTIC ANEMIAS.

WITH PARTICULAR REFERENCE TO THE NATURE OF SPHEROCYTOSIS
AND INCREASED FRAGILITY.*†

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IN 3 successive cases of acute non-familial hemolytic anemia, active serum isohemolysins were discovered which were capable of hemolyzing red cells of their own type and of Group O.¹⁶ These isohemolysins presented all the classical criteria of immune bodies: inactivation by heat, reactivation by the addition of complement, slightly increased activity after storage in the ice-box for several hours, somewhat diminished activity after prolonged storage in the ice-box, and a positive Ehrlich-Morgenroth phenomenon. In addi-

* Aided by a grant from the Charlton Fund, Tufts College Medical School.

† Read before the American Society for Clinical Investigation, Atlantic City, N. J., May 2, 1938.

tion, inactivation could be effected by incubation of the serum with normal serum. In the first 2 cases, which were subacute in type, the blood picture was "pseudomacrocytic," careful analysis indicating that most of the large red blood cells were reticulocytes and not orthochromatic macrocytes. These cases were completely refractory to blood transfusions, but dramatic recoveries took place when splenectomy was performed. In the third case, the blood picture was microcytic, being characterized before splenectomy by the presence of marked spherocytosis and greatly increased fragility of the red cells in hypotonic salt solutions. With improvement of the patient after splenectomy, spherocytosis gradually diminished and finally disappeared, the erythrocyte fragility became normal, and the hemolysins could no longer be demonstrated.

As these cases were studied, several possibilities suggested themselves: 1, that acute hemolytic anemia and possibly other hemolytic syndromes might be due to the action of hemolysins; 2, that the differences in the type of hemolytic reaction might be a matter of degree and dependent upon the "dosage" of hemolysin; and 3, that spherocytosis and increased fragility might be due to the action of hemolysin rather than dependent upon a disturbed formation of red cells in the bone marrow. In order to test these possibilities, it was decided to reproduce hemolytic anemia experimentally by the use of a hemolytic serum immunologically similar to that found in our clinical cases. The production of immune hemolysins by the injection of the red cells of one animal species into the blood stream of another has been practised almost since the beginning of immunologic studies. By this means a heterophilic hemolytic serum is produced which, when injected into the donor animal species, will result in the production of hemolysis. Because the guinea pig is readily available for hematologic studies and its red cells are so similar in nature to those of man, it was chosen for the donor species. The rabbit was used for the production of an anti-guinea pig hemolytic serum. Although the production of hemolytic anemia by this method has been accomplished by other investigators in the past, exact hematologic studies and their correlation with clinical syndromes have not hitherto been fully carried out. The results of of these studies are the subject of the present paper.

Methods and Material. 1. *Preparation of Hemolytic Sera.* Adult guinea-pigs weighing about 500 gm. were used. They were fed on a mixed diet of hay, seed, lettuce, carrots, and so on. Heart blood was obtained by puncture of the ether-anesthetized animal and washed with normal salt solution. The blood was then injected into the ear veins of rabbits in accordance with the following scale of dosage: 1st day, 0.5 cc.; 3d day, 1.0 cc.; 5th day, 1.0 cc.; 7th day, 1.0 cc.; 11th day, 1.5 cc. On the 19th day a trial bleeding was performed, and the rabbit serum titrated for anti-guinea pig hemolytic activity *in vitro*. The hemolytic titer at this time usually varied between 1 to 50 and 1 to 100, the agglutinin titer between 1 to 200 and 1 to 400. If the serum was sufficiently potent, it was inac-

tivated by heating to 56° C., for $\frac{1}{2}$ hour, and phenol 0.4% was added as a preservative. All hemolytic serum was diluted to a final titration value of 1 to 50 (normal rabbit serum has a guinea pig hemolytic activity of under 1 to 10). Sera of high titer, up to 1 to 1600, have been prepared by the use of more frequent injections and by continuing injection over a longer period of time. The hemolytic sera thus prepared presented all the criteria of an immune serum which have been listed above. As with the human hemolytic serum, hemolytic activity could be inactivated by incubation with normal guinea-pig serum.

2. *Titration of Hemolysin.* The hemolytic sera were diluted 1 to 2, 1 to 4, 1 to 8, 1 to 16, 1 to 32, and so on. To 0.5 cc. of serum were added 0.5 cc. of a 2% suspension of washed guinea-pig red cells, 1.5 cc. of isotonic (0.85%) NaCl solution, and 0.5 cc. of a 10% fresh guinea-pig serum for complement. These materials were mixed and incubated at 37° for an hour before readings were made. The hemolytic titer was given by the last tube in which hemolysis was visible, the agglutinin titer by the last tube in which agglutination was visible.

3. *The Production and Study of the Hemolytic Syndromes.* Guinea-pigs were injected intraperitoneally and intramuscularly with varying doses of standardized (1 to 50) hemolytic serum, comparative studies with both methods of injection being made. Control injections with normal rabbit serum were also performed. Hematologic studies were made frequently, usually at daily intervals. Blood was obtained in small drops from one of the ear vessels. Hemoglobin estimations were made by the Newcomer method, so calibrated that 100% equaled 15.5 gm. of hemoglobin. Red blood cell and white blood cell counts were made with U. S. Bureau of Standards certified pipettes and hemacytometers. Platelet counts were performed according to the method of Dameshek.¹⁵ Reticulocyte counts were performed in the ordinary "dry" manner on cover slips, brilliant cresyl blue and Wright's stain being used. Price-Jones curves^{42b} were performed by counting 200 red cells, using a calibrated Leitz micrometer eyepiece. Hematocrit estimations were made by using Heller and Paul's dry oxalate mixture³⁰ for collection of the blood and the Wintrobe⁴⁹ hematocrit tubes. Estimations of the mean red cell thickness were made from the mean corpuscular volume and red cell diameter according to the following formula:

$$\text{Thickness} = \frac{\text{volume}}{\text{surface area}} = \frac{\text{mean corpuscular volume}}{\pi (\text{radius})^2}$$

In the determinations of hematocrit and fragility, separate sets of guinea-pigs were usually used because of the necessity of removing 2 cc. of heart blood at 1 to 3-day intervals. Fragility tests were performed according to the method of Daland and Worthley,¹³ so modified that only a 10% suspension of red blood cells was used.

Postmortem examinations were performed in every instance. Smears from the bone-marrow were stained with Wright-Giemsa stain; sections of the bone-marrow and spleen were fixed in Zenker's solution, paraffin sections being prepared and stained with eosin-methylene blue.

Results. 1. *The Effect of Normal Rabbit Serum.* When normal rabbit serum was injected into guinea pigs (Chart 1), the effect was entirely negative except for minor fluctuations in erythrocyte counts and for slight reticulocytosis.

2. *The Comparative Effect of Intraperitoneal and Intramuscular Injections.* Identical small, medium and large doses of hemolytic serum were given intramuscularly or intraperitoneally to three sets

of 6 guinea pigs and their effects compared. In general, the effects were identical, the only difference being in the rapidity of the development of the hemolytic syndrome. Serum given intraperitoneally produced anemia more quickly, and with large doses resulted more quickly in death of the animal than when the injections were given intramuscularly. As judged from the survival times of the animals, the intraperitoneal route was 1.5 to 2 times as effective as the intramuscular. Intravenous administration was not attempted.

3. *The Comparative Effects of Various Dosages of Hemolytic Serum.* Varying dosages of hemolytic serum were given to 56 guinea pigs. The type of hemolytic effect produced varied directly with the amount of serum injected (Chart 2).

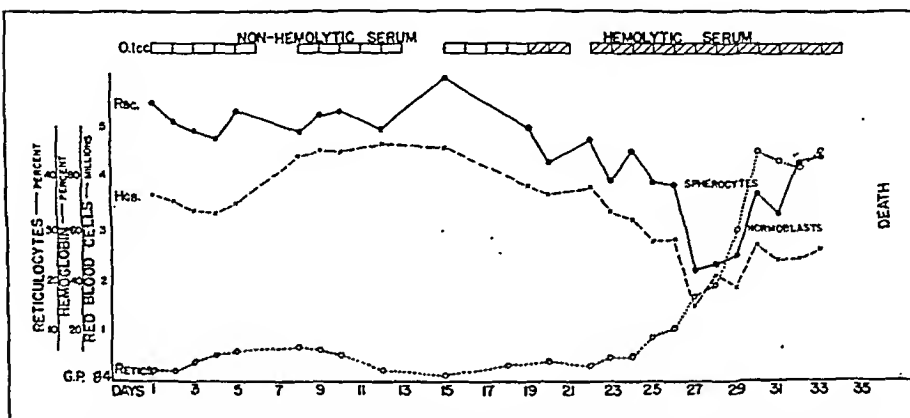


CHART 1.—The effect of (a) normal rabbit serum, and (b) hemolytic rabbit (anti-guinea pig) serum on the red blood cells and hemoglobin of the guinea pig.

The effect of the normal serum is negligible, whereas the hemolytic serum produces intravascular hemolysis with anemia and a compensatory reticulocytosis.

(a) *Large Dosage.* Doses of hemolytic serum varying between 0.5 and 2 cc. were given to 27 guinea pigs. This usually produced death within 5 days. In almost every instance, a fulminating anemia resulted, which was characterized by the presence of an almost uniformly microcytic type of cell population and a greatly increased erythrocyte fragility. Very little evidence of bone-marrow regeneration in the form of reticulocytosis was present, and at postmortem examination hemoglobinuria was a striking feature. In 5 cases a less fulminating acute hemolytic anemia with less marked microcytosis developed.

(b) *Medium Dosage.* Nineteen guinea pigs received moderately large dosage: 0.2 cc. of hemolytic serum daily or increasing daily doses of serum beginning with 0.1 cc. up to 0.7 cc. Usually an acute hemolytic anemia resulted, although in 1 case a fulminating anemia developed as with the larger dosage, while in 5 cases a rela-

tively subacute type of anemia ensued. Occasionally definite anemia did not develop. In the majority of these cases, the erythrocyte count dropped to levels of about 1,000,000 in a period of 5 to 7 days. The outstanding hematologic feature in these animals was the development of small, thick red cells ("spherocytes") which became prominent about the 3d to the 5th day after injection. This phenomenon was associated with marked increase in erythrocyte fragility. Within a day or two after the most marked spherocytosis, reticulocytes became prominent, in some cases reaching a level of 50 to 56%, and nucleated red cells appeared. Spherocytes now became diminished both in relative and absolute numbers, and the blood picture became dominated by the appearance of large red cells, usually reticulated. The animals now either made an uneventful recovery or died.

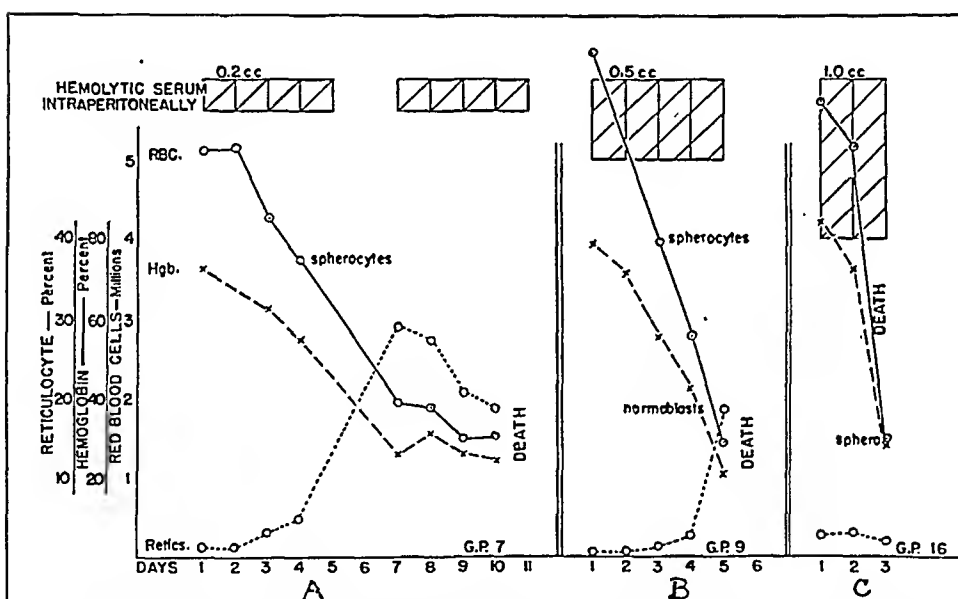


CHART 2.—The effect of varying doses of hemolytic serum on the red blood cells.

A small dosage results in (a) a gradually progressive anemia with secondary well-marked regenerative changes (reticulocytosis); (b) moderate dosage in acute hemolytic anemia; and (c) large dosage in fulminating anemia with hemoglobinuria but without reticulocytosis.

(e) *Small Dosage.* Eleven guinea pigs were given small doses of hemolytic serum—9 animals 0.1 cc. daily, and 2 animals 0.1 cc. twice weekly. There were no demonstrable effects in the 2 animals of the latter group, whereas in those given daily injection, all developed subacute anemia. The "subacute anemia" which was less rapid in its development than the acute type was similar in its hematologic picture to the terminal reaction of the acute syndrome, *i. e.*, there was moderate anemia of 3,000,000 to 3,500,000, and very little spherocytosis, the blood picture being dominated by the

presence of nucleated red cells, reticulocytes and normal-sized red cells ("pseudomacrocytic" blood picture). In these cases the anemia ordinarily persisted for about 2 to 3 weeks, following which the animal usually made a complete recovery.

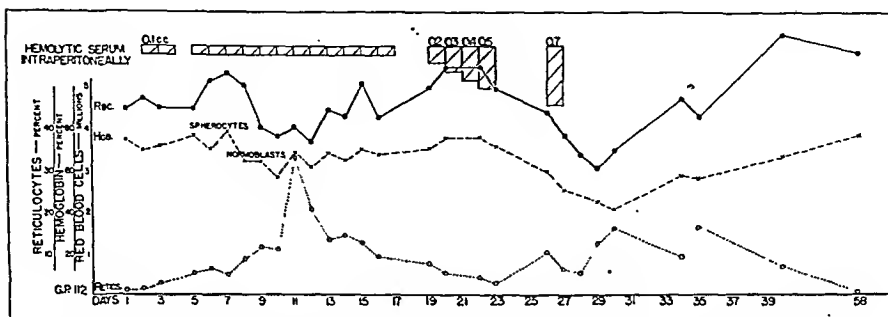


CHART 3.—The effect of increasingly large doses of hemolytic serum after several injections of small daily dosages.

Despite the relatively large dosages, a precipitous drop in red blood cell count does not develop, probably because of the protective action of a previously stimulated bone marrow. This effect may be contrasted with the findings recorded in Chart 4.

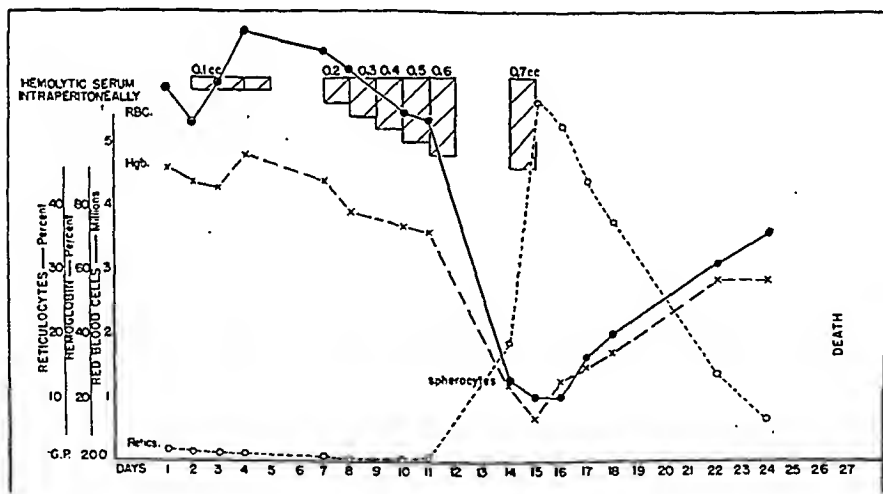


CHART 4.—The effect of increasingly large doses of hemolytic serum. There is a rapid drop both in red cell count and hemoglobin, quite in contrast to the changes noted in Chart 3, in which the animal was given preliminary small doses of hemolytic serum.

(d) *The Effect of a Small Dose of Hemolytic Serum Followed by a Large Dose.* In 1 guinea pig, small doses (0.1 cc. 1–50) of hemolytic serum were given intraperitoneally daily for 16 days with the resultant development of subacute anemia (Chart 3). Beginning with the 18th day, the daily dosage of serum was increased by 0.1 cc. until 0.7 cc. was given. This resulted in a moderate degree

of anemia with only slight reticulocytosis (16%), the animal making a complete recovery. This is quite in contrast with the reaction of the animals receiving increasing daily dosage of hemolytic serum up to 0.7 cc., *without* preliminary small injections; in these, the development of acute hemolytic anemia was the rule (Chart 4).

4. *The Blood Picture.* As pointed out above, the blood picture varied directly with the dosage of hemolytic serum injected—a large dose producing a rapidly fulminating anemia with hemoglobinuria, a medium-sized dose producing an acute hemolytic anemia, and a small dose a subacute type of syndrome.

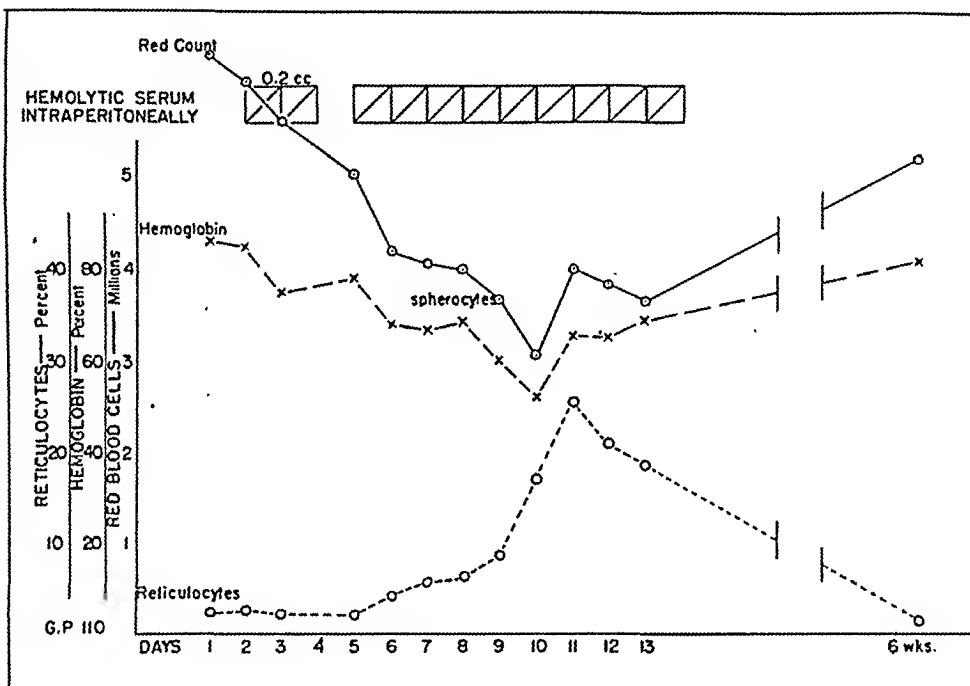


CHART 5.—The effect of moderate daily doses of hemolytic serum. A subacute type of anemia develops. Note the well-marked reticulocytosis which is followed by gradual rise in the erythrocyte and hemoglobin level. Spherocytosis develops with progression of the anemia.

Red Blood Cell Counts. The normal red cell count of the guinea pig varies between 5,000,000 and 6,000,000 per c.mm., and the normal hemoglobin concentration between 13 and 15 gm. per 100 cc. In the fulminating cases the red cell count dropped precipitously. Within 1 to 2 days the count fell to 1,000,000 or less with a concomitant fall in hemoglobin, and the animal died. In the less fulminating cases, the red cell count fell less precipitously, reaching its lowest level of 1,000,000 or thereabouts in a period of 5 to 7 days, following which the animal either died or began to show recovery. In the subacute cases, the development of anemia took place relatively slowly over a period of 7 to 14 days, and the anemia was less profound with the red cell count usually dropping to a level of

about 3,000,000 to 3,500,000. Following the persistence of an anemic level for several days, there was gradual increase in erythrocyte count while the animal made complete recovery (Chart 5).

Type of Red Cells. The red cells of the normal guinea pig are identical in appearance with those of man, being round, and when viewed on edge, biconcave in appearance. There is slight anisocytosis, but the great majority of cells have a diameter between 7 and 7.5 micra, the average red cell diameter being 7.2 micra. With the development of anemia, marked changes in the size and shape of the red cells took place, the most striking change being in the development of microcytosis (Chart 6). The microcytes were further characterized by an appearance of increased thickness, clearly visible in the stained preparations, and unusually well-brought out in the supravital preparations. When seen on edge, these cells presented a striking appearance of roundness, the biconcave appearance having completely disappeared and the cell having assumed a spherical character. Supravital studies on these preparations revealed that the red cell goes through a series of distinct changes before becoming a "complete" spherocyte. At first the biconcavities become more shallow. Then one concavity disappears, leaving cup-shaped or jug-shaped cells with an indentation which becomes progressively more shallow. When this disappears, a round ball-shaped "spherocyte" results. The more sudden and severe the anemia, the greater was the proportion of these cells. In the fulminating cases, the animal died with practically 100% spherocytes, the rare reticulocytes appearing huge in comparison. In those with longer course, the red cell picture shortly became diversified, due to the appearance of large, biconcave, polychromatophilic red cells which, when stained supravitaly, were seen to be reticulocytes. At the same time nucleated red blood cells (normoblasts) of varying degrees of maturity and in varying numbers were seen, together with other signs of increased regenerative activity on the part of the bone marrow: basophilic stippling, ring bodies, and so on. The striking contrast between the small thick spherocytes and the immature cells (reticulocytes) was at no time greater than at this point, when both types of cells were present in great abundancy (Chart 7). In this stage both rapid hemolysis and well-marked regenerative activity were present. In cases which went on to recovery the spherocytes gradually disappeared as more and more reticulocytes and new mature red cells appeared, and with their disappearance the blood picture assumed a "pseudomacrocytic" appearance with an actual increase in the average red cell diameter (*q. v.*). This was due to the presence of large numbers of polychromatophilic macrocytes (reticulocytes), and of normal new red cells. With recovery of the animal, the blood picture finally resumed its normal appearance.



Normal

Hemolytic phase

Regenerative phase

Acute experimental hemolytic anemia.

CHART 6.—Changes in the erythrocyte picture in the peripheral blood of a guinea pig following daily injection of large doses of hemolytic serum.

The hemolytic phase (4th day) is characterized by the presence of extreme microcytosis (spherocytosis), while the regenerative phase (7th day) is marked by the appearance of large new cells (reticulocytes) which appear huge in contrast. Note that the spherocytes have a thick appearance even in dry films and show no central concavity. ($\times 940$.)



Hemolytic phase

Regenerative phase

Recovery phase

Subacute experimental hemolytic anemia.

FIG. 7.—Changes following daily injections of moderate doses of hemolytic serum.

The hemolytic phase (7th day) is characterized by a moderate spherocytosis. In the later phases of regeneration and recovery the large reticulocytes give a false picture of macrocytosis ("pseudomacrocytic" picture) similar to that seen in certain cases of clinical acute hemolytic anemia. Note that the new red blood cells (reticulocytes) but recently derived from the bone marrow are large. ($\times 940$.)

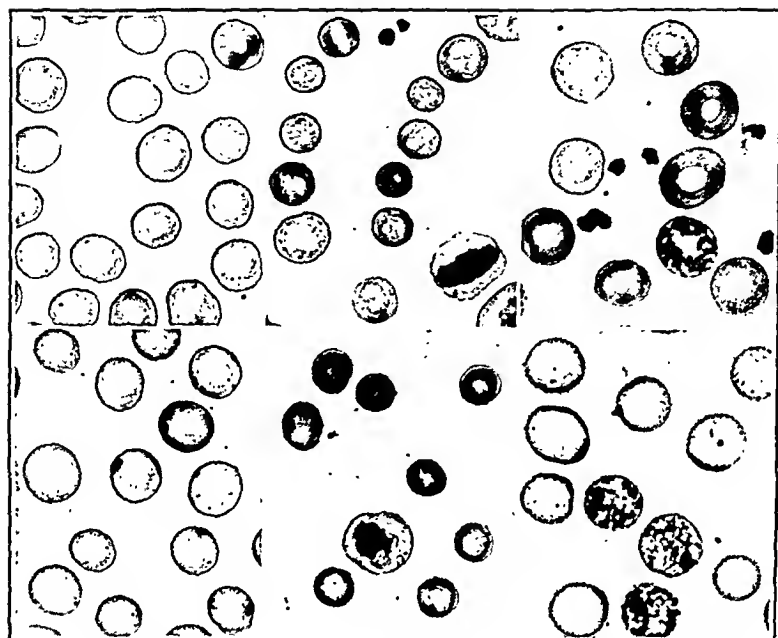
Normal

Case 3

Case 2

A

B



Normal

Acute experimental

Subacute experimental

CHART 12.—Similarities in the blood pictures of the guinea pig (B) and man (A) normally, in acute hemolytic anemia and in subacute hemolytic anemia.

Note the spherocytosis in the middle set of pictures and the pronounced reticulocytosis characteristic of the subacute course both clinically and experimentally. (X 940.)

Reticulocytes. In the acute fulminating cases, the animals frequently died with severe anemia and without the appearance of reticulocytes. The less acute cases were characterized by varying degrees of reticulocytosis, most marked in the subacute cases which

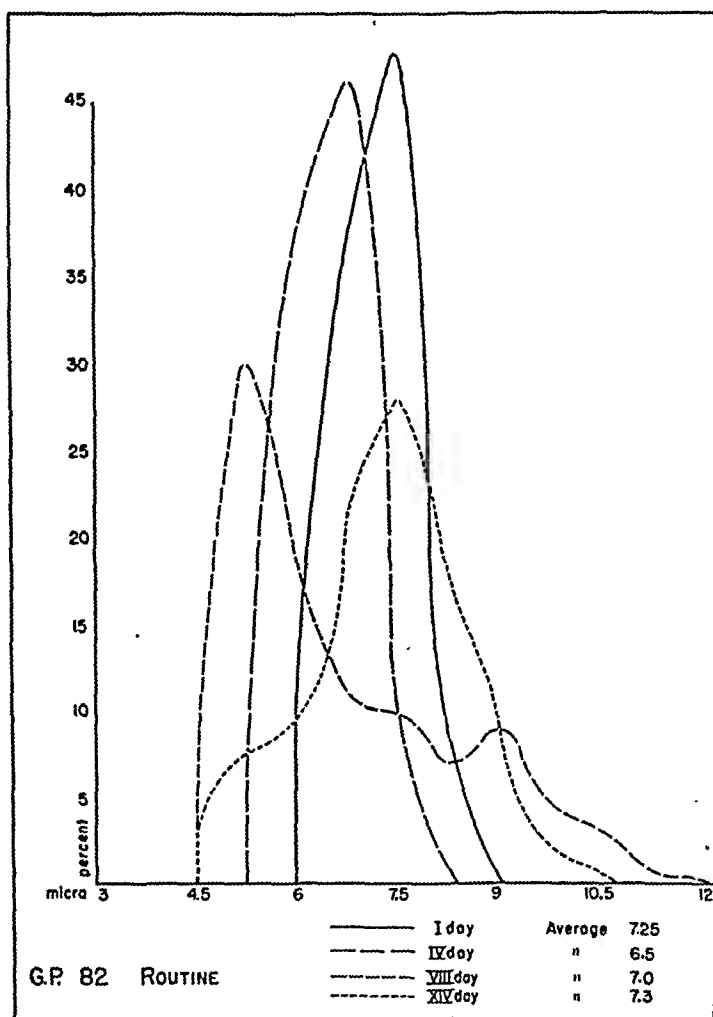


CHART 8.—Price-Jones curves of the red blood cell diameters during the development of anemia following the injection of hemolytic serum.

Note that the first change is a uniform shift (4th day) to a smaller type of red cell population. Next (8th day) is further diminution in the cell size with the appearance of well-marked spherocytosis. Simultaneously one notes the appearance of large cells (reticulocytes) (see also Chart 9). This gives a peculiar "hump"-shaped curve. Finally (14th day) is a shift to a normal type of curve, although a heterogeneity of all the red cell population (wide curve) is still to be noted. (Guinea pig No. 82.)

went on to recovery. In these animals reticulocyte counts of 40 to 56% were common. Following the reticulocyte peak the red count usually rose.

Price-Jones Curves. The varying and often rapid changes in the types of red cells are best brought out in studying the red cell

diameters by the Price-Jones method. The first change which developed became noticeable in 1 to 3 days and was characterized by a shift to a smaller type of mature red cell population, the average red cell diameter diminishing to about 6.8 micra (Chart 8). With further diminution in the average red cell diameter to between 5 and 5.6 micra, anemia became increased. The very small cells

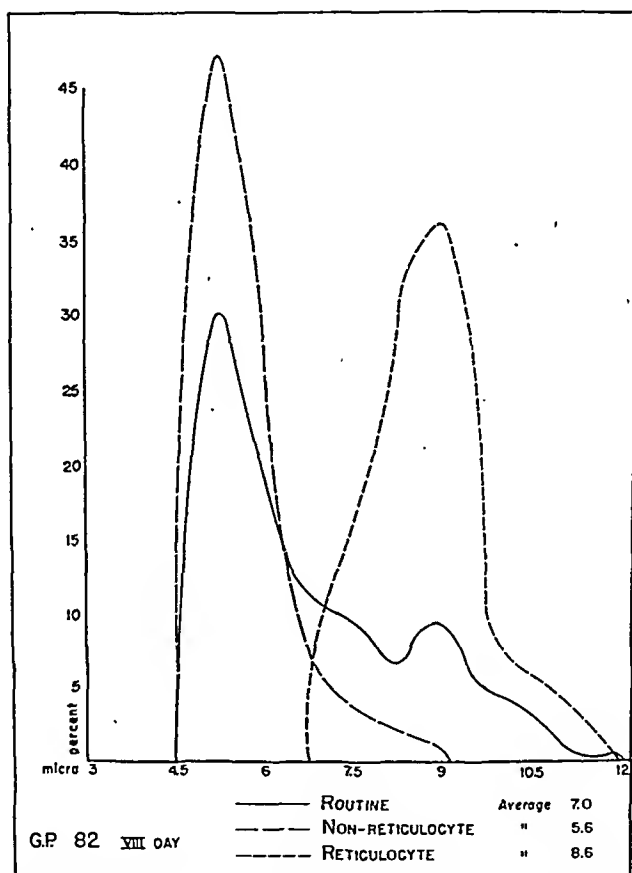


CHART 9.—Analysis of the Price-Jones curve of the red cell population on the 8th day (see Chart 8).

It will be seen that the formerly normal cells have almost entirely been reduced to microcytes (spherocytes) and that the apparent increase in large cells and consequent increase in average cell diameter is produced by the appearance of normal-sized reticulocytes. Guinea pig No. 82.

were all spherocytes. In those animals which survived this period, the next change that occurred was characterized by a double-peaked Price-Jones curve. Analysis of this curve by differential diameter counts of reticulocytes and non-reticulocytes (Chart 9) demonstrated that the largest peak, which was at a smaller cell diameter than normal, was caused by the mature red cells (mostly spherocytes), and the smaller peak, present at a larger red cell diameter

than normal, was composed of reticulocytes. With recovery, the curve might at first show a macrocytic tendency, which then gave way to an essentially normal type of curve.

Hematocrit, Mean Corpuscular Volume, Mean Cell Thickness. The volume of packed red cells of the normal guinea pig varies between 46 and 50%. When a moderately large dose of hemolytic serum was given, a definite diminution in the hematocrit was noticeable within 24 hours, and within 48 hours there was a precipitous drop to levels between 25 and 32%. With the development of severe anemia, the hematocrit value reached levels of between 11 and 20%. The mean corpuscular volume of the normal guinea pig is somewhat smaller than that of the normal human, varying in our cases from 73 to 82 cubic micra. Although the hemoglobin and red cell levels diminished rapidly, no definite change took place in the mean corpuscular volume; in fact, this might actually become increased: from 73 to 89 cubic micra in one instance, from 81 to 87 cubic micra and from 73 to 87 cubic micra in other instances.

Despite this essential lack of change, or even increase, in the total cell volume, the diameter of the red cells was simultaneously diminishing rapidly. This could indicate only one thing: a marked increase in the thickness of the individual red cell. Calculation of the mean cell thickness from the mean cell volume and the mean cell area showed a marked increase in this factor: from 1.79 to 4.2 micra (!) in 1 case in which the animal died with practically all spherocytes, and from 1.9 to 3.01 micra in another instance (Table 1).

TABLE 1.—CORRELATION OF CERTAIN ERYTHROCYTIC FACTORS.

Dose (in cc.).	Days.	R.B.C. (in mill.).	Hematocrit. %.	M.C.V.	M.C.D.	M.C.T.	Fragility (% NaCl).	
							B.H.	C.H.
<i>G.P. 88. Large Dose—Acute Fulminating Anemia.</i>								
0.3 . . .	0	6.90	49.5	73	7.3	1.79	0.40—0.24	
0.3 . . .	1	5.45	44.5	82	7.0	2.11	0.40—0.26	
0.3 . . .	2	3.81	28.0	74	6.0	2.70		
	3	2.50	18.0	72	5.8	2.71	0.80—0.32	
	4	1.56	14.0	89	5.2	4.20	+0.80—0.40	
<i>G.P. 89. Medium Dose—Acute Anemia.</i>								
0.2 . . .	0	5.70	42.0	74	7.0	1.90	0.46—0.30	
0.2 . . .	1	5.04	38.0	76	6.8	2.09	0.48—0.28	
0.2 . . .	2	4.79	39.0	81	6.6	2.34	0.46—0.28	
	5	4.76	38.0	80	5.8	3.01	0.56—0.32	
	6	4.39	37.0	84	6.0	2.99	0.58—0.20	
	7	4.11	36.0	87	6.2	2.89		
	8	3.89	32.0	81	6.2	2.69	0.52—0.12	
	9	4.32	32.0	78	7.1	1.94	0.50—0.12	

M.C.V. = mean corpuscular volume.

M.C.D. = mean corpuscular diameter.

M.C.T. = mean corpuscular thickness.

B.H. = beginning hemolysis.

C.H. = complete hemolysis.

With diminishing hematocrit percentage, the mean cell volume remains normal or even increased but the mean cell diameter becomes greatly diminished. Thus the mean cell thickness becomes greatly increased and simultaneously, the fragility of the red cells becomes abnormally great.

Fragility. The erythrocyte fragility was studied in 12 instances. In the normal guinea pig, hemolysis began at 0.4 to 0.5% of NaCl solution, and was complete at 0.2 to 0.3%. Average figures for beginning and complete hemolysis were 0.44 to 0.24%. The fragility test following administration of hemolytic serum varied directly with the amount of serum given, *i. e.*, with the type of hemolytic syndrome induced (Chart 10). In the fulminating cases, with the development of severe anemia, hemolysis began at or just below the concentration of normal salt solution (0.8 to 0.85%), becoming complete at 0.4%. In the less fulminating acute cases, fragility

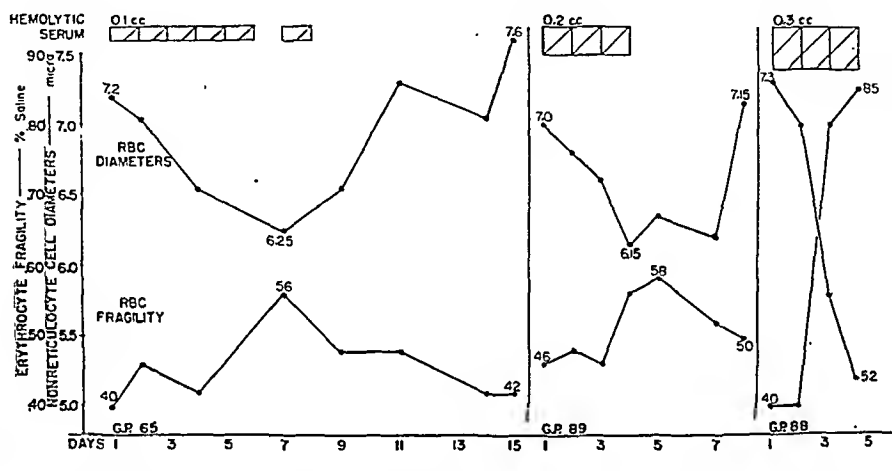


CHART 10.—The effects of varying doses of hemolytic serum on cell diameters and fragility (resistance to hypotonic solutions of sodium chloride) of the red cells.

A large dose of hemolysin results in a precipitous drop in the red cell diameter and a greatly increased fragility; smaller doses result in less dramatic changes. In guinea pig No. 65, given the smallest dose, an actual increase in red cell diameter develops in recovery, with an associated return of the erythrocyte fragility to normal. There is striking correlation between the development of microspherocytosis and increasing fragility. The spherocyte (and its associated phenomenon: increased fragility) may be considered as an index of intravascular hemolysis.

rapidly increased to values of 0.58 to 0.68%, following which it would diminish unless the animal died. In the "subacute" cases, fragility became only slightly increased, hemolysis beginning at 0.5 to 0.56%. As the animal recovered, the fragility test returned to its normal level; in fact, in some instances, increased resistance of the red cells developed with hemolysis beginning at 0.38% NaCl and becoming complete at 0.1 to 0.12%.

The changes in fragility test could readily be correlated with the various morphologic changes occurring in the red cells. Thus, with extreme fragility, as in the fulminating cases, almost all of the red cells were spherocytes; with moderately increased fragility,

the spherocytes were not as numerous; and with slightly increased fragility, relatively few of the cells were present. These correlations are graphically brought out by comparison of beginning hemolysis in the fragility test with the average red cell diameter of the non-reticulocytes (Chart 10). It is seen that increasing fragility varied directly with diminishing diameter of the mature red cells and with their increasing thickness; diminishing fragility developed as the

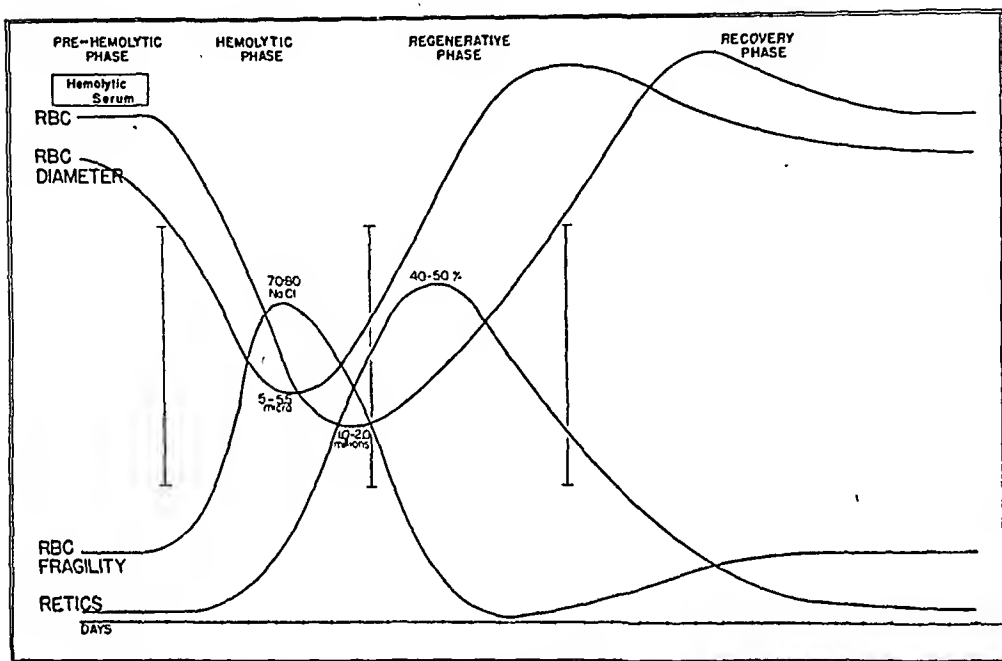


CHART 11.—Semidiagrammatic chart of the various phases which take place in the experimental hemolytic anemia produced by the injection of hemolytic serum.

During the "prehemolytic" stage the only demonstrable change is slight diminution in the average diameter of the red cells. This is the stage of "sensitization." Following this (hemolytic phase), as the red cells shrink further and become more markedly spherocytic, there is an accompanying decrease in the resistance of the cells with a rise in the fragility. The spherocytes now begin to disintegrate with resultant fall in the red cell count. As a compensatory measure the bone marrow becomes hyperactive (regenerative phase) and reticulocytes appear. With the appearance of the reticulocytes, there is an increase in the cell diameter, which may actually become greater than normal (pseudomacrocytic blood picture). Simultaneously with the outpouring of new cells, there is a rise in the red cell count. During the period of regeneration when the old (destroyed) cell population is entirely replaced, the resistance of the new cells is found to be increased. The recovery phase is characterized by gradual return of all the factors to their normal levels.

red cell diameter increased. The phase of increased resistance which might develop during recovery was associated with the development of the "pseudomacrocytic" type of blood picture, in which large numbers of reticulocytes and normal new red cells were present (Chart 11).

5. *Pathologic Anatomy.* In the fulminating cases there was evidence of severe "toxicity" with occasional areas of ecchymosis, hemorrhagic areas in the lungs, and reactions of necrosis about the

site of the intramuscular injection. These were lacking in the "acute" and "subacute" cases. The spleen in all types was invariably enlarged—from $1\frac{1}{2}$ to 5 times its normal size—and microscopically showed extreme congestion, with dilatation of sinusoids. The bone marrow was intensely hyperplastic, the hyperplasia being limited mainly to the erythroblastic elements. Erythrogenesis was of the "normoblastic"¹⁷ type, the immature red cells being similar to those seen in functional hyperplasia following hemorrhage. Differential counts of bone-marrow smears bore out the marked hyperplasia, as evidenced by the numerous erythrogonocytes and the normoblasts of the "A" (macroblast) variety.¹⁷ Price-Jones diameter studies of the nucleated red cells of the bone marrow showed that the most mature nucleated red cells (Type "C") were normal in size, even in those animals which had died of the fulminating syndrome with practically 100% of spherocytes present. In other words, the discrepancy in size between the relatively large normoblast "C" (normoblast) of the bone marrow (as well as of the peripheral blood, when present) and the spherocyte of the blood was a striking phenomenon which will be commented upon below.

Comment. 1. *Previous Studies.* The production of hemolytic anemia by the use of heterophilic hemolytic serum is almost as old as the science of immunology. Belfanti and Carbone² were apparently the first to carry out this procedure. Bordet,³ and Ehrlich and Morgenroth²⁰ used this method in developing their theories of immunity. Cantacussène,⁵ and Lesné and Ravaut³⁵ established the different effects of large and small doses. Panton and Ross,¹⁸ confirmed by Muir and McNee,³⁹ demonstrated that large doses caused hemoglobinemia and hemoglobinuria, whereas small doses produced nucleated red cells and many microcytes. Banti,¹ in 1913, distinguished two phases in the experimental hemolytic anemia: hemolytic, characterized by diminution in red cell count and hemoglobin; and regenerative, characterized by the presence of large numbers of reticulocytes. Banti also demonstrated the appearance of marked fragility of the red cells which developed as the anemia progressed. From 1913 to 1937 few investigations were apparently carried out with this method. Filo,²³ in 1937, produced hemolytic anemia by the use of heterolytic sera and, although he carefully studied the erythrocyte, leukocyte and platelet counts, he made but little attempt to correlate this work with clinical phenomena, nor did he study the red cell diameter or fragility.

In summary, although previous investigations in the production of various hemolytic syndromes by the use of heterolytic sera have been moderately extensive, they are deficient from the hematologic standpoint in that most of the studies were made as part of an immunologic research. The work of Panton and Ross,¹⁸ Banti,¹ and of Filo²³ is thoroughly in line with our own investigations, although the significance of the various hematologic findings does

not appear to have been appreciated. Thus all but Banti noted the pronounced microcytosis, but failed to attach any significance to it. Banti dismissed the increased fragility by concluding that it was due to the development of a special "fragilizing" activity by the organism. He discounted the possibility that the increased fragility might be due to the action of the hemolysin upon the red cell, as suggested by Troisier, Dufourt and others.^{45b} In none of the investigations was the spherocytic character of the red cell or its relationship to the increased fragility mentioned.

2. *Dosage and Classification.* It has been demonstrated that by simple variation in the dosage of hemolytic serum various types of hemolytic syndromes can be produced. Thus large dosage resulted in fulminating anemia and hemoglobinuria; moderate dosage, in acute hemolytic anemia in which initially spherocytosis and later reticulocytosis were prominent; small dosage, in a relatively chronic or subacute anemia, in which bone-marrow regeneration often overshadowed the evidences of hemolysis. These three types were not always as clear-cut as thus delineated, since transition types could occasionally be distinguished. Preliminary experiments in the production of chronic hemolytic anemia in the guinea pig have not as yet been successful.

The various types of hemolytic syndromes experimentally produced may readily be matched with well-known clinical syndromes, often described under different headings, and supposedly completely unrelated. These are compared in the accompanying table:

TABLE 2.—HEMOLYTIC SYNDROME AND DOSAGE OF HEMOLYSIN.

Experimental syndromes.	Clinical syndromes.
<i>Large Dosage.</i>	
A. Fulminating hemolytic anemia with hemoglobinuria	Acute paroxysmal hemoglobinuria; ^{37,38} paroxysmal nocturnal hemoglobinuria; ^{12,27} fulminating acute hemolytic anemia with hemoglobinuria; hemoglobinuria with hemolytic anemia. ⁸
<i>Moderate Dosage.</i>	
B. Acute hemolytic anemia:	Acute hemolytic anemia ("febrile," "Ledercr's"); ^{11,22,25,34,36}
(a) With spherocytes predominating.	(a) With spherocytes predominating.
(b) With reticulocytes predominating	(b) With reticulocytes predominating; "crisis" of chronic hemolytic anemia; ? erythroblastosis fetalis.
<i>Small Dosage.</i>	
C. Subacute hemolytic anemia with "pseudomacrocytic" blood picture	Subacute hemolytic anemia ^{11,22,25,34,36} with "pseudomacrocytic" blood picture (often mistaken for pernicious anemia); hemolytic anemia and "pernicious anemia" of pregnancy.
D. Chronic hemolytic anemia (not yet produced)	Chronic hemolytic anemia: With spherocytic blood picture (congenital); ? with sickle-cell blood picture.

By analogy with the experimental syndromes, one may speculate that differences in clinical syndromes are due, at least in some measure, to differences in the degree of intravascular hemolysis which is taking place. By thinking of the various clinical hemolytic syndromes in terms of "dosage" of hemolysin, one can readily see why hemoglobinuria may accompany certain cases of fulminating acute hemolytic anemia, why hemolytic icterus is an accompaniment of certain cases classified as "hemoglobinuria," and why "crises," resembling in every respect the clinical picture of acute hemolytic anemia, occasionally occur in cases of chronic congenital hemolytic icterus.

Hemoglobinuria is merely the signpost of a hemoglobinemia that rises above the kidney's threshold for blood pigment. Hemoglobinemia develops when intravascular hemolysis is so rapid that conversion of hemoglobin to bilirubin cannot take place rapidly enough to prevent its detection in the blood stream. Chauffard⁸ pointed out this fact in 1909 and stressed the relationship of dosage of hemolysin to the character of the resultant syndrome. Thus, in the case of Chauffard and Vincent,⁸ in which acute hemolytic anemia was present in association with a very active serum hemolysin, hemoglobinuria and icterus were both present. In paroxysmal "cold" hemoglobinuria (associated with the Donath-Landsteiner type of hemolysin) intravascular hemolysis is apparently so rapid that icterus, which takes time to be produced, does not develop³⁷ in detectable amounts. In paroxysmal nocturnal hemoglobinuria,³⁸ hemoglobinuria is outstanding at night whereas during the day only icterus and hemoglobinemia are present. The report of Hamburger and Bernstein,²⁷ which stresses the relationship between hemoglobinuria and icterus, points out the common fallacy of regarding cases of hemoglobinuria as belonging to an entirely different category from that of hemolytic anemia (icterus). Hemoglobinuria and hemolytic icterus are simply different manifestations of the same fundamental phenomenon: intravascular hemolysis. Rapid fulminating hemolysis causes hemoglobinemia (and hemoglobinuria); less rapid hemolysis results only in icterus (and usually anemia).

3. *The Blood Picture.* (a) *General.* As shown above, the variations in the blood picture were directly dependent upon the dosage of the hemolytic serum and upon the phase of the resultant hemolytic syndrome. Thus, with *large dosage* the blood picture in these cases was a purely hemolytic one and completely lacking in regenerative phenomena. *Medium-sized dosage* resulted in (a) a hemolytic phase with many spherocytes, and (b) a regenerative phase with prominent phenomena of erythrocytic immaturity. *Small dosage* resulted in an inconspicuous hemolytic phase, soon overshadowed by the phenomenon of regeneration, turning gradually to normal.

(b) *The Spherocyte*. The most outstanding feature of the blood picture was the development during the hemolytic phase of large numbers of small, thick red blood cells, *i. e.*, *spherocytes*. These cells exhibited all the characteristic criteria: microcytosis, an appearance of increased density and thickness in the stained preparation, a definitely rounded and globular appearance in the fresh preparations with disappearance of the normal biconcavity, a greatly increased thickness with an equally increased volume-thickness index, and finally increased fragility (see below).

The spherocyte was first described as such by Naegeli⁴⁰ in cases of congenital hemolytic icterus. He suggested that these cells were pathognomonic of the disease which could thus be designated as "spherocyte anemia" or "globe-cell anemia." Gänsslen²⁴ made much the same observations, but correlated the spherocyte and increased fragility. Microcytosis (small diameter) had previously been described by Chauffard¹⁰ and numerous other observers. Von Boros⁴ was the first to make careful studies of the increased thickness of the microcytes and showed that, although the cells were diminished in diameter, the cell volume was nevertheless normal. This could only be explained by increased thickness. Von Boros also proposed a "thickness index" to indicate the degree of change in thickness. Haden²⁶ studied these phenomena further and concluded that "Naegeli's conception of microspherocytosis as the fundamental and probably constant inborn error in this disease (congenital hemolytic icterus) seems the correct one." He stated that "the shape of the red cell indirectly represents an anatomic variation from normal," in common with the "tower skull" and other abnormalities. Gänsslen, Naegeli and Haden all concluded that the microspherocytosis indicated a definite bone-marrow defect and was pathognomonic of the disease. Thompson⁴⁴ states: "The, spherical microcytes . . . are as pathognomonic of this disease as are the sickle cells, in sickle-cell anemia." On the other hand, von Boros⁴ and Heilmeyer²⁹ state that they have observed the spherocyte in various conditions other than congenital hemolytic icterus.

Our own experience, both in clinical and in experimental cases, is directly contrary to the view that spherocytosis is primarily due to a bone-marrow defect. We were led to the view that spherocytosis might be due to the activity of a hemolytic agent in the serum by the findings in our third case of acute hemolytic anemia,¹⁶ which was characterized by the presence of large numbers of spherocytes and increased fragility (Chart 12). In this case, as the titer of hemolysin diminished, the red cell diameter increased and the erythrocyte fragility became normal. Similar cases have previously been described by Chauffard, Troisier and Girard,⁹ and by Widal and Weissenbach.⁴⁷ In previous studies of Henstell and Dameshek³¹ of the bone marrow and blood in a case of congenital hemolytic

icterus, it was noted that the red cell diameter of the most mature nucleated red cells in the bone marrow averaged 9.84 micra (normal or slightly increased), whereas the average red cell diameter of the peripheral blood was reduced to 6.76 micra. Furthermore, the most mature nucleated red cells in the peripheral blood of the clinical case of acute hemolytic anemia above referred to were of normal diameter: 8.9 micra, as compared with the average cell diameter of the non-reticulocyte red cells of the same day: 6.85 micra. The average cell diameter of the reticulocytes in this case was 8.16 micra, whereas that of the non-reticulocytes (mature red cells) was reduced to 6.18 micra. These clinical findings, demonstrating that the immature red cells of the bone marrow and peripheral blood, were of normal size while the mature red cells were distinctly smaller than normal, could only indicate that the spherocytes were formed not in the marrow but by the action of some agent on circulating red blood cells. Support of these views was given in our animal experimentation.

In the experimental hemolytic syndromes, the number of spherocytes varied directly with the dosage of hemolytic serum, *i.e.*, the larger the dosage, the greater the number of spherocytes. The Price-Jones curves brought out graphically the changes which developed in the mature circulating red cells as hemolysis took place. These changes have been discussed in detail above. The nucleated red cells of the peripheral blood were always normal in size and nucleated microcytes were never encountered. Studies of the red cell diameters of the most mature nucleated red cells of the bone marrow, in animals dying with almost total microspherocytosis of the peripheral blood, gave normal values for the bone-marrow cells. In an animal dying of acute fulminating hemolytic anemia, for instance, the average diameter of the most mature normoblasts was 9.3 micra (normal), whereas there was extreme microcytosis of the peripheral blood with an average cell diameter of 5.2 micra. We feel that these findings show conclusively that: *a*, spherocytes are formed outside of the bone marrow; *b*, spherocytosis develops only in mature red cells; *c*, a hemolytic agent, such as is present in hemolytic sera, is responsible for its development. As a corollary to these views, the ideas that spherocytosis is pathognomonic for congenital hemolytic jaundice and indicative of an inherited bone-marrow defect are cast into question. We have been able to produce spherocytosis in animals by other hemolytic agents, such as distilled water and phenylhydrazine. Price-Jones,^{42a} and Kaminer and Rolnstein⁴² also noted that microcytosis became prominent during the phase of hemolysis in experimental hemolytic anemia produced by this drug. Banti¹ noted microcytosis and increased fragility in animals given toluol diamine. In clinical reports of hemolytic anemia due to such agents as malaria and sulphanilamide, the microcytosis is pointed out, without much attention being paid

to the phenomenon. For example, careful inspection of the photomicrograph in Harvey and Janeway's²⁸ recent article on acute hemolytic anemia due to sulphanilamide will reveal the presence of several typical spherocytes.

We feel, therefore, that spherocytosis represents an alteration in the mature red cell brought about by various types of hemolytic agents. In congenital hemolytic icterus, the spherocytosis may be due to the more or less continued action of an hemolysin. The extreme spherocytosis of the crisis of this disease may be due to the sudden liberation of large amounts of hemolysin and the resultant action upon the mature red cell.

(c) *The Reticulocyte and the Pseudomacrocytic Blood Picture.* It may be stated as axiomatic that whenever there is increased blood destruction, increased blood formation shortly takes place, unless, of course, the marrow is incapacitated. So much is this the case, that the reticulocytosis of hemolytic anemia is recognized as an important part of the blood picture and of diagnostic significance. In general, the more active the hemolytic process, the more marked is the reticulocytosis. This is brought out in the cases of congenital hemolytic icterus, in which fluctuations in severity of the disease are accompanied not only by changes in bilirubin content of the serum, urobilinogen content of the urine and extent of spherocytosis of the red cells, but also in the percentage of reticulocytes. In certain cases of acute hemolytic anemia, reticulocytosis is often so pronounced as to dominate the blood picture. Since the reticulocytes (polychromatophilic red cells) are always somewhat larger than the mature erythrocytes, the blood smear in these cases will often appear to be that of a macrocytic anemia. Analysis of the type of red cell population by differential Price-Jones curves of reticulocytes and non-reticulocytes shows that the appearance of macrocytosis is given by the reticulocytes. Thus in the second of our cases of acute hemolytic anemia (L. G.) (Chart 12), the average red cell diameter was 7.6 micra; the average diameter of the mature red cells (non-reticulocytes) was, however, 7.28 micra, and that of the reticulocytes 8.33 micra. The mean corpuscular volume in this case at the same time was definitely elevated—125 cubic micra. We have called this type of blood picture "pseudomacrocytic," since, although it resembles superficially the blood picture of pernicious anemia, it is not truly macrocytic in the same sense.

This pseudomacrocytic type of blood picture was readily reproduced in our animal experiments and was noted in the phases of regeneration and beginning recovery (Chart 12). One may conclude from the animal experiments that the finding of a similar picture in the clinical cases is indicative of active hemolysis with simultaneously active regeneration on the part of a functionally hyperplastic marrow.

(d) *The Fragility Test.* Chauffard,¹⁰ in 1907, was the first to demonstrate that the red cells of congenital hemolytic icterus were unusually fragile to hypotonic salt solutions. He felt that this was the fundamental abnormality of the disease. The nature of the increased fragility was for many years a mystery. Troisier,⁴⁵ Dufourt¹⁹ and others felt that the increased fragility might be due to "sensitization" of the red cells by hemolysin with consequently increased fragility. Banti, who produced experimental hemolytic anemia and demonstrated increased fragility, was at a loss to explain this phenomenon and suggested that the animal developed a "fragilizing" quality in the process. Gänsslen²⁴ was the first to suggest a definite relationship between the presence of spherical erythrocytes and increased fragility. Haden's²⁶ investigations confirmed this work and placed it on a firm basis. He further emphasized the direct correlation between thickness of the red cells and their susceptibility to hemolysis. Ponder,⁴¹ and Castle and Daland⁶ studied the problem extensively. These recent investigations have abundantly shown both that the increased fragility of the erythrocytes in congenital hemolytic icterus is due to their spherical nature, and that the extent of spherocytosis is directly correlated with the volume-thickness index.

Previous studies of the dynamics of the problem have always been made either by producing spherocytosis *in vitro* by the use of hypotonic solutions or from study of several cases of congenital hemolytic jaundice with variable cell thicknesses. In our own experiments a more dynamic method was utilized, in that we were able to study the changing fragility simultaneously with the changing relationships in the red cell count, red cell size and reticulocyte percentage. As already pointed out above, these studies have shown a striking correlation between the development of spherocytosis and increasing fragility. The red cells become unusually susceptible to hemolysis by hypotonic salt solutions when their average diameter is reduced and their average thickness increased. On the other hand, with increasing cell diameter and diminishing cell thickness, the cells became more resistant to hemolysis. Finally, with the development of a "pseudomacrocytic" blood picture in which reticulocytes were the outstanding cells, the red cells actually became more resistant than normal to hypotonic salt solution.

These results are confirmatory of the previous investigations referred to above. In addition, they have the advantage of having been performed in the experimental animal, where with rapidly altering conditions in the type of red cell present the fragility test could be frequently carried out. They confirm conclusively that the fragility test is merely an expression of the average thickness of the red cell. The increased resistance of the red cells which developed during the phase of marked reticulocytosis is interesting in view of the many contradictory opinions which have been ad-

vanced regarding the fragility of the reticulocytes. As Daland and Zetzel¹⁴ have pointed out, opinion is about evenly divided that the reticulocyte is (a) more resistant and (b) less resistant than the normal red cell. Our investigations show quite clearly that the reticulocyte is more resistant than the normal red cell. Further studies on this point are now in progress.

The studies of Gänsslen²⁴ and of Haden²⁶ showed that increased fragility is a function of the spherocyte. Our own investigations have further demonstrated that spherocytosis is a function of the action of hemolytic agents. We feel therefore that increased fragility is indicative of a hemolytic process and not simply evidence of an anatomic peculiarity of the red cell.

4. *The Relationship of Hemolysins to Hemolytic Anemia.* That various syndromes closely comparable to those seen clinically can be produced by hemolytic sera has been demonstrated. The question may be raised whether the experimental types necessarily bear any significant relationship to the clinical cases. We feel that although there is no proof of the identity of the clinical and experimental syndromes, the evidence is in favor of such a concept. We cite the following: 1, The serum in our 3 cases of acute hemolytic anemia showed the presence of an active "immune" hemolysin which disappeared as the patient recovered. 2, The hemolytic serum used in our experiments corresponded in every immunologic respect to the serum of our clinical cases. 3, The experimental hemolytic syndromes were similar in every respect to the clinical types. 4, Hemolysins have been found in various hemolytic syndromes.

1. Our finding of active isohemolysins in 3 cases of acute hemolytic anemia was a rediscovery, since Chauffard and Troisier,⁷ Chauffard and Vincent,⁸ Widal and his collaborators,⁴⁸ and several others⁴⁶ had pointed this out in the years between 1907 and 1914. Krumbhaar,³³ in his review of the subject, published in 1915, referred to these findings. Furthermore, both Chauffard⁹ and Widal⁴⁷ had observed single cases in which, with diminution in titer of hemolysin, there was subsidence of anemia and diminution in the abnormal fragility of the red blood cells. This fact in Case 3 of our series led to the speculation that the hemolysin might be etiologically related to the disease and the cause of the spherocytosis. The finding of hemolysin in the serum might simply be due to the production of an excess in the tissues with resultant overflow into the blood. The hemolysin which was present gave all the reactions of an immune body and had thus been probably produced in response to an unknown antigen.

2. The hemolytic serum produced experimentally by the injection of guinea-pig erythrocytes into the rabbit possessed all the various characteristics of immune hemolysin and was thus immunologically identical with the human hemolytic serum of the clinical cases.

The same reactions took place in both sera with heat, addition of complement and addition of normal serum.

3. The experimental syndromes which could be produced by varying the dosage of hemolytic serum were identical with various clinical syndromes (see Table 1). Hemoglobinuria, acute fulminating hemolytic anemia, subacute hemolytic anemia could all be reproduced. Although similarity of syndrome does not necessarily indicate a similar etiologic agent, it is nevertheless suggestive, especially when the experimental hemolytic serum is comparable immunologically to that found clinically. The further findings in the experimental cases of spherocytosis, increased erythrocyte thickness and increased fragility together with the development of reticulocytosis, "pseudomaerocytic" blood picture and splenomegaly, were all confirmatory of our main thesis that the various features of the hemolytic anemias are all due to the action of hemolysins.

4. Hemolysins have been found in various clinical hemolytic syndromes. In all, five types of hemolysins have been described: 1, That of paroxysmal hemoglobinuria, in which, as Donath and Landsteiner³⁷ pointed out, an hemolysin activated by cold was present; 2, that described by Salén⁴³ in a case of paroxysmal hemoglobinuria as heat stable and not requiring complement; 3, that of paroxysmal nocturnal hemoglobinuria in which, as described by Dacie, Israëls and Wilkinson,¹² a heat-labile, non-complement requiring hemolysin was found in low titer; 4, Enneking's²¹ auto-hemolysin and isohemolysin in paroxysmal nocturnal hemoglobinuria; 5, and finally, the heat-stable, complement-requiring immune hemolysin described by Chauffard and his collaborators and by the present authors in cases of acute, non-familial hemolytic anemia.

Summarizing this line of thought, since hemolytic syndromes identical with those seen clinically may be produced experimentally by immune hemolytic serum, and since hemolysins are occasionally found in clinical cases, the possibility exists that the various clinical hemolytic syndromes are due to the action of hemolysins. These may be of different types and may be present in different amounts. They may function slowly, and produce a relatively chronic process; or violently, and produce a hemolytic "crisis." That the various hemolytic syndromes are due fundamentally to the activity of hemolysins upon mature circulating red blood cells and not to altered cellular formation in the bone marrow has not been definitely proven, although the evidence cited above indicates that the latter possibility is extremely remote.

Summary. 1. Isohemolysins of the immune-body type were discovered in the serum of 3 cases of acute hemolytic anemia.

2. Anti-guinea pig hemolytic serum was prepared by the injection of guinea pig red cells into rabbits. This serum possessed all the immunologic properties of the serum found in the clinical cases.

3. Hemolysis of the red cells of the guinea pig *in vitro* followed the injection of this serum.

4. By varying the dosage of anti-guinea pig hemolytic serum, various types of hemolytic syndromes were produced: fulminating hemolytic anemia with hemoglobinuria, acute hemolytic anemia and subacute hemolytic anemia.

5. Various types of blood pictures could be reproduced at will: microspherocytosis, increased erythrocyte fragility, reticulocytosis, "pseudomacrocytic" blood picture and so on.

6. The spherocyte is a small thick red blood cell unaltered in volume though small in diameter and unusually fragile to hypotonic salt solutions. Our observations point to the conclusion that spherocytosis is due to the activity of hemolysin and not to an abnormal anatomic peculiarity or to a disturbed formation of cells in the bone marrow. Since increased fragility is a function of the increased thickness of the red cell, it is dependent upon the same cause.

7. We believe that hemolytic syndromes are due to hemolysins, possibly of different types and present in different amounts, functioning slowly in some cases and violently in others. The various blood pictures of the hemolytic anemias, *viz.*, anemia, spherocytosis, increased fragility, reticulocytosis, are in all probability due to the effects of the varying activity of hemolysins, and modified by the individual's power to react.

8. Since the experimentally produced hemolytic syndromes and the numerous clinical types are closely comparable, the chief differences in the clinical syndromes may be a matter of the amount of functioning hemolysin present.

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PAROXYSMAL HEMOGLOBINURIA.

WITH REPORT OF A CASE.*

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THE subject of this communication (1473-36) is a sailor, aged 33, who reported to the Outpatient Department of the Montreal General Hospital in March, 1936, because of severe chills followed by the voiding of wine-colored urine.

Clinical History. The family history was not relevant.

The patient himself had smallpox at the age of 17 and a gonorrheal urethritis at 24, but otherwise enjoyed perfect health. He denied syphilis by name or symptom.

The illness for which he sought treatment began in the autumn of 1935. Following exposure to cold, he had a shaking chill lasting an hour, followed on 2 consecutive occasions by voiding wine-colored urine. Since the initial attack he has had 5 or 6 rigors, each following exposure to the cold. Subsequent chills were more severe than the first. The attacks lasted from 3 to 4 hours, were characterized by chattering of the teeth and all the usual phenomena of a severe rigor. They were not at once relieved by blankets or the external application of heat. Each chill was followed by the voiding of 1, 2 or 3 specimens of wine-colored urine. At no time was there frequency, burning or painful micturition. He lost 14 pounds during the winter but considered his health normal in the intervals between attacks.

Physical examination was negative in every respect. There was no obvious anemia; no adenopathy; no enlargement of liver or spleen, and the

* Read by title before the Association of American Physicians, May 5, 1936, by the late Prof. Campbell P. Howard.

heart and lungs were normal on both physical and skiagraphic examinations. The blood pressure was consistently low, averaging systolic 90, diastolic 40. There were no stigmata of syphilis. The urine examination on admission was quite normal but the blood Wassermann test was strongly positive. Blood urea, creatinine, sugar and cholesterol were within normal limits. The Van den Bergh was 0.2 units and the urine urobilinogen present in less than one-tenth dilution—both normal values. Pyelograms showed the kidneys to be normal in size, shape and position.

During the patient's stay in the hospital typical attacks were produced by chilling the hands and feet in ice water for 30 minutes. Shorter periods of chilling or chilling of hands or feet alone failed to produce an attack.

The presence of autohemolysins in blood plasma was demonstrated by means of the Donath-Landsteiner reaction. This test consists in chilling a mixture of the patient's serum (inactivated), a dilute suspension of his washed erythrocytes, and complement (guinea-pig's serum), for a period of 10 minutes. When the mixture is heated to body temperature hemolysis occurs if autohemolysins are present. The same mixture unchilled does not show hemolysis.

The first Donath-Landsteiner test on the patient was made on March 16 shortly before the initial experimental chilling which consisted in immersing his hands and feet in ice water for 30 minutes. The blood serum was normal in appearance. The mixture of inactivated serum, washed cells and complement was chilled for 10 minutes in ice water then incubated for 15 minutes at 37° C. No hemolysis occurred. Following immersion the blood serum became bright red in color and showed spectroscopically the bands of oxyhemoglobin. The urine at the end of the period of exposure was clear but 5 minutes later it was brown in color; 30 minutes later it was port-wine colored. This dark color began to clear in 3 hours and the specimen voided 4 hours after immersion was clear. No red cells were present in the urine specimens, though the benzidine test for blood was strongly positive. Spectroscopic examination showed that the red color of the urine was due to hemoglobin. On March 20, 4 days later, the Donath-Landsteiner test was repeated, the routine of the test being altered as in Table 1:

TABLE 1.—DONATH-LANDSTEINER TEST, MARCH 20, 1936.

Test mixture.	Ice-water chilling.	Warming.	Result.
I. Patient's serum — washed R.B.C.—Comp. . . .	None	37° C. 2 hrs.	No hemolysis
II. Patient's serum — washed R.B.C.—Comp. . . .	10 min.	37° C. 2 hrs.	Half R.B.C.s hemolyzed in 2 hrs.
III. Patient's serum — washed R.B.C.—Comp. . . .	30 min.	37° C.	Immediate complete hemolysis
IV. Patient's serum—Group IV R.B.C.—Comp. . . .	13 min.	37° C. 2 hrs.	Incomplete hemolysis
V. Patient's serum—Group IV R.B.C.—Comp. . . .	30 min.	37° C.	Immediate complete hemolysis

The Donath-Landsteiner test of March 20 showed not only that the patient's blood serum contains autohemolysins, that is, hemolysins for his own erythrocytes, but also that the serum will cause hemolysis of any other red cells in the same group. It contains isohemolysins as well as autohemolysins. It demonstrated further that the technique of the test must be altered to meet varying degrees of susceptibility to chilling. In this instance the test carried out on March 16, according to approved technique, was quite negative. By lengthening the time of chilling of the blood serum

TABLE 2.—CHANGES OCCURRING *e Frigore* AND AFTER A CHILL.

Time.	Urine.					Blood.														Fragility R.B.C.s.					
	Appearance.	Sp. gr.	React.	Alb.	R.H.C.	Benz.	Mier.	R.B.C.	W.B.C.	Hb.	Platelets.	Cell diam.	Differential.					Plasma color.	Van den Bergh.		Liver.	Spleen.	Temp.		
													P.	Ly.	Eos.	Mono.	Cell vol.							Sed. rate.	
9.55	Yellow	0.14	Ac.	0	0	0	0	4	09	16	1	93	183	7.7	75	18	3	2	45%	0.6 mms.	Light yellow	0	0	98 ²	0.475 to 0.375
9.55*																									
10.35	Amber	...	Ac.	+	0	2+	0	0	0	98 ²	
10.35†																									
11.00	Dark wine	...	Ac.	3+	0	4+	Many gran. casts	3.64	8	5	80	68	28	1	1	42%	0.45	Light red	1.0	96 ³	0.475 to 0.375
11.00‡																									
12.00																									
1.00	3.65	17.8	82	141	7.7	87	9	1	1	Red	..	Palp.	Palp.	100 ³	
3.00	Brown red	0.01	Ac.	+	0	3+	Few gran. casts	Palp.	Palp.	99 ³	
5.00	Amber	0.00	Ac.	+	0	Tr.	Occ. gran. cast	Palp.	Palp.	99 ³	
7.00	Yellow	0.06	Ac.	Tr.	0	0	0	Yellow	..	0	0	97 ⁴	

* Hands and feet immersed in ice-water for 35 minutes.
 † After generalized shaking and chattering of teeth. Exposed parts white. Vessels constricted.

in the second test on March 20 the result was strongly positive. These findings agree with the clinical observations that chilling of one arm and one foot, or even the two feet or two hands, was insufficient to bring about a rigor. Definite chilling of both hands and feet was necessary to produce an attack.

The dramatic nature of the onset of the chill and the changes which took place during the rigor are briefly summarized in Table 2. It is to be noted that hemoglobinuria was present slightly before the time of onset of the chill and before external heat was applied. At no time were red cells found in the urine, though the benzidine test on the pigmented specimens was strongly positive and the spectroscopic showed the bands of oxyhemoglobin. The presence of albumin and granular casts during the excretion of the hemoglobin may indicate that the latter had an irritant effect on the kidneys during excretion.

The patient subsequently received one 3 months' course of antiluetic therapy, then disappeared for a year. During that interval of time no chills occurred, although he spent the winter in Montreal.

Discussion. The disease is seldom encountered. Only 1 other case was found in the records of the Montreal General Hospital between the years 1898 and 1936 during which time there were 209,879 admissions. A majority, though not all cases, have syphilis. The history is characteristic. The patient experiences rigors after chilling which are, however, not followed by any great degree of fever. Wine-colored urine is noted commonly at the first voiding after the chill and it persists for some hours. After the cessation of hematuria no symptoms are experienced until again exposed to chilling.

Physical examination, if made between attacks, reveals no characteristic abnormality. After severe chills slight to moderate anemia of the orthochromic type is commonly present. In our case, after 2 recent rigors, the erythrocyte count was 4.09 millions. During the third chill, reported in detail here, the erythrocyte count dropped from 4.09 to 3.65 million per c.mm. Roughly estimated, this represents a destruction of approximately 10% of the total circulating erythrocytes, and gives some idea of the degree of hemolysis. That this hemolytic upheaval is intimately associated with the reticulo-endothelial tissues is suggested by the temporary enlargement of liver and spleen during and immediately after the chill. The diagnosis in suspected cases can be made with certainty by one or other of the methods employed in our case. The attacks can be produced experimentally by chilling hands and feet in ice water. Prolonged chilling of both hands and feet may be necessary in mild cases. Confirmation of the character of the pigment in blood and urine is obtained by means of spectroscopic examination. The Donath-Landsteiner reaction is positive in all cases. It should be recognized, however, that some modification of the established technique may be necessary in mild cases to fix the antibodies to the erythrocytes. This point has already been referred to in this report.

Treatment in the syphilitic cases consists in vigorous antiluetic therapy. As in our case, it is usually successful in preventing or diminishing the number of attacks. Dickson¹ reported a case which remained well for at least 13 years after antiluetic treatment.

The nature of the changes which take place during the rigor and the exact mechanism of their production are not definitely known. During chilling of the hands or feet constriction of the cooled skin vessels brings about sufficient slowing of the blood stream to permit lowering of the temperature of the blood in the constricted vessels to a point not greatly above that of the skin. When the temperature of the blood in the capillaries of the chilled extremities is sufficiently reduced, the antibodies become attached to the erythrocytes. Hemolysis occurs when these red cells leave the cooled areas and are warmed to body temperature. This is precisely what happens *in vitro* during the Donath-Landsteiner test. The abolition of the hemolytic process during the spinal anesthesia or after section of the sympathetic nerves to the chilled parts,² which presents vasoconstriction during chilling, is further proof of the foregoing hypothesis.

Summary and Conclusions. 1. A case of paroxysmal hemoglobinuria *e frigore* is reported.

2. The disease was apparently arrested by antiluetic therapy.

3. The technique of the Donath-Landsteiner reaction should be modified to meet varying degrees of susceptibility to chilling.

4. Temporary enlargement of liver and spleen may occur during the attack.

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THROMBOSIS—A MEDICAL PROBLEM.

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WHEREAS thrombosis (including embolism therefrom) has long been accepted as a hazard in surgery, trauma, and obstetrics, its recognition as an equally important hazard in the management of strictly medical patients seems tardy and inadequate. At this hospital its not infrequent occurrence among patients on the medical service impelled a review of the hospital's experience with this condition. Sudden death of a normally convalescent surgical patient on the 10th postoperative day with postmortem disclosure of a massive pulmonary thrombosis merely revealed a dreaded but not unfamiliar manifestation of this surgical hazard. Sudden death

of a medical patient, like Case 35:115, who had undergone three major operations on previous admissions without thrombosis, while currently hospitalized on the medical service for arthritis, with post-mortem disclosure of a similar pulmonary thrombosis, demonstrated its less familiar independence of surgical provocation. Such occurrences resulted in the compilation of data on all cases of thrombosis (and embolism therefrom) which had come to postmortem examination during the first 13 years of the hospital's existence (October 2, 1924, to October 2, 1937).

During this period 2613 postmortems were performed averaging 201 yearly, and representing 70% of all deaths in the hospital. Under the technique routinely employed, and with frequent restrictions regarding the head, cord, or other areas, possibly some thrombi (particularly cerebral, portal, popliteal) remained undetected. Thrombosis of the hemorrhoidal plexuses, probably the most frequent site of spontaneous thrombi in human beings was not included, nor were minor thrombi, except when their site lent them importance, as in the coronary or cerebral vessels. Yet in spite of any restriction of method and of limited postmortem examination, and the exclusion of minor thrombi, the condition was encountered in 648 patients—approximately one-quarter of the entire postmortem series. There were 427 strictly medical patients, only 195 were surgical, and 26 comprised a miscellaneous group of obstetric, traumatic, fracture, dislocation and dental cases.

Some mention should be made of the selectivity of patients and diseases in this hospital. Relatively, the hospital admits more old, chronic, rural, cardiac, neoplastic and surgical cases, and fewer young, acute, urban, obstetric and traumatic cases than the average general hospital. The average age at death within the hospital has dropped during 13 years until now it is 7 years below that for the state generally. The main causes of death within the hospital—cardiac, cancer, pneumonia—coincide with those for the state and nation as a whole. In considering therefore whether the findings are typical or merely locally peculiar, these qualifying circumstances should be borne in mind.

To show more clearly the incidence, distribution, and importance of thrombosis among the three classes of patients data on these items have been collected into the large Table 1. Many findings have been omitted which may have been interesting in other respects but proved irrelevant to the objective of portraying thrombosis as an increasingly apparent medical menace. Some of the general characteristics of thrombosis not incorporated in the chart will be briefly considered, followed by some of its contradictory characteristics.

General Characteristics. 1. *Incidence.* The most surprising characteristic of thrombosis is its frequency. Finding 648 cases among 2613 autopsies gives a higher percentage (24%) than in most series.

Bela,³ in 6581 postmortems between 1913 and 1933 at the City Hospital, Kiel, Germany, found 926 cases (14%); Cleland⁶ found 190 cases among 3000 autopsies at Adelaide, Australia (6.3%); Wantoch,²³ 367 cases among 4739 posts at Basel, Switzerland (7.7%). However, coronary thromboses were included in this series, and a complete microscopic examination was made in all cases.

TABLE 1.—THROMBOSIS AND EMBOLISM AMONG 2613 POSTMORTEMS, WISCONSIN GENERAL HOSPITAL, 1924 TO 1937.

	Medical cases. 427.	Surgical cases. 195.	Miscellaneous cases.* 26.	Total cases. 648.
Sex:				
Male	287	140	16	443
Female	140	55	10	205
Size:				
Gross	300	118	19	437
Microscopic	127	77	7	211
Number:				
Single	265	135	16	416
Multiple	162	60	10	232
Main sites:				
Pulmonary	226	98	17	341
Cardiac (mural)	117	23	..	140
Pelvic	48	23	3	74
Aorta	40	12	4	56
Inguinal (ileo-femoral)	33	13	6	52
Coronary	36	4	..	40
Renal	24	13	..	37
Cerebral	16	4	3	23
Operative site	29	..	29
Miscellaneous	88	40	..	128
Associated diseases:				
Cardiac: primary	203	5	..	208
secondary	135	94	7	236
Cancer	96	90	1	187
Blood dyscrasias	11	1	..	12
Infection: present	114	112	10	236
absent	313	83	16	412
Effect:				
Incidental finding only	165	94	11	270
Morbidity of varying degree	141	63	6	210
Fatal: with sudden death	70	23	5	98
without sudden death	51	15	4	70
With record of previous surgery without thrombosis	142	75	1	218

* Of the 26 patients composing this group, 5 were obstetrical cases, 12 had fractures, 2 had teeth extractions, and 7 had various other types of trauma.

Probably equally as surprising is its preponderance among strictly medical cases. Two-thirds (427) of the cases were medical patients unexposed to the hazards of surgery, obstetrics, or trauma, on the current admission. The fact that 142 of them had previously undergone operations without thrombosis and 19 more gave records of uneventful pregnancies or fractures should not be overlooked.

Classifying patients solely as "medical," "surgical" or "miscellaneous," while desirable for the sake of simplicity, nevertheless continually entails difficulties. The following cases illustrate these

difficulties: Case 35:101, recumbent for 4 months following operation, dies suddenly of pulmonary thrombosis. Shall the operation (surgical factor) or the prolonged recumbency (medical factor) be indicated? Case 35:118 dies later in the day following a craniotomy for brain tumor, with the disclosure at postmortem of a large potentially dangerous inguinal thrombosis. Shall the severe operation or the mechanical pressure of Poupart's ligament plus other local factors be blamed? While these and similar cases were all placed in the surgical classification, they nevertheless indicate the difficulty of making clean-cut classifications, and the importance of medical, or non-surgical factors in postoperative thrombosis.



FIG. 1.—Massive pulmonary embolism. Pulmonary artery opened to show coils of a long laminated thrombus.

Attempts to compute the incidence of thrombosis among the three types of patients (medical, surgical, miscellaneous) also proved unsatisfactory. The postmortems, for example, represented only 70% of the deaths. In view of the many postmortem cases in which thrombosis was disclosed as an incidental, or at least a non-fatal finding, it seemed fair to assume that it had also occurred frequently in patients who recovered. During the period of 13 years covered, there were 99,469 admissions to the hospital, 68,260 operations, and 2142 deliveries; the exact number of casts applied was not available but very probably exceeded 20,000.

2. *Associated Diseases.* One answer to the question why a patient who has undergone surgical operation without thrombosis on a previous admission now dies of thrombosis on the medical service without surgery lies in the main associated condition, namely, cardiovascular disease. In the medical group, 203 patients out of 427 had various types of cardiac disease as the primary condition and 135 more as an important secondary condition. In the surgical group, 5 patients had a primary cardiovascular condition and in 94 more it was an important secondary condition. The disproportion between the two groups in the number of cardiac thrombi is striking. Among the medical patients, many of whom had serious primary heart ailments, 117 out of 427 (28%) revealed this type of thrombosis, the relationship of which to cardiac disorders is well established. Among the surgical patients, only 5 of whom had a primary heart ailment, only 23 out of 195 (8%) revealed it. Among the 26 miscellaneous patients, there was not one case.

Another indication of the relationship of cardiovascular disease to thrombosis is that of the 218 patients in the entire series who now developed thrombosis after avoiding it in previous operations, 179 now had cardiovascular disease as the primary or an important secondary condition. Case 35:278 affords a simple illustration: this 50-year-old male underwent an appendectomy uneventfully 2 years ago; 1 year ago he contracted acute rheumatic fever with cardiac involvement; now hospitalized for the cardiac condition, he dies suddenly of bilateral pulmonary thrombosis with three mural thrombi in the right auricle.

Among the entire series of 648 cases, the principal cardiac lesions were found to the following extent: decompensation with chronic passive congestion of viscera, and so forth, 336 cases; cardiac hypertrophy, 316 cases; hypertension on admission, 153 cases; old or recent rheumatic inflammation of the heart, 114 cases. Only 23 of the 648 cases revealed syphilitic stigmata, reflecting the low incidence of this disease in the state of Wisconsin.

While the preponderance of cardiovascular disease throughout the series tends to simplify the problem, certain other conditions tend to complicate it. In contrast to the abundance of cardiovascular disease is the scarcity of *blood dyscrasias*. In this series at least, two of the accepted factors in thrombogenesis, alteration in the blood current and alteration in the vessel wall, outweigh the third factor, alteration in blood content. Of the various leukemias, anemias, purpuras, and Banti's disease, there were only 12 cases among the 648. The incidence of these diseases among all autopsies is considerably higher, inasmuch as the special interest of the hospital in blood dyscrasias is well known throughout the state. Anemia secondary to some other condition was fairly common. No instance of embolism occurred as a consequence of the injection treatment of *hemorrhoids* or *varicose veins*. Complete thrombosis

of the iliac artery was found in 1 case treated with *thyroid* extract for postoperative hypothyroidism. Several cases of thrombosis were found in diseases of the biliary system, with marked *jaundice* and delayed coagulation time.

Infection of tissues, such as gangrene, abscess, cellulitis, and erysipelas, was present in a majority of surgical cases, in a smaller proportion of medical and miscellaneous cases. Aschoff,¹ reviewing the war-time study of thrombosis made by Dietrich,⁷ admitted the very important rôle played by infection in such thrombosis, although he believed that even in war-time thrombosis static factors such as blood loss, debility, bandaging, paralysis often played a part. In this series of peace-time thrombosis, infection ranks far behind stasis.

Cancer was present in almost half of the surgical cases, but in less than one-quarter of the medical cases. Cancer may exert a thrombogenic influence: 1, indirectly through its general or constitutional effect on the patient—altered resistance, metabolism, debility, secondary anemia, infection, and so forth; 2, through its interference with adequate liver production of heparin; and, 3, directly by its encroachment on vessels; and, 4, dispersal of cancer cells in the blood stream. In several instances cancer cells were seen within the structure of the thrombus. Cancer patients as a rule, however, maintain an elevated metabolic rate, supposedly one of the protective factors against thrombosis.

3. *Wide Range.* Another characteristic of thrombosis is the wide range it traverses, not only with regard to size, numbers, age of patients, and composition, but also with regard to distribution, time of occurrence, clinical manifestations, and most important of all, its effect on the patient. As examples of unusual *composition* in addition to the cancer-containing thrombi mentioned above, the thrombi in 1 case contained within themselves hematopoietic centers, those in another case contained bone. In *distribution*, while found predominantly in certain locations where mechanical factors most handicapped the circulation—the heart chambers, the aorta, the pulmonary arteries, the pelvic veins, and the inguinal arteries and veins—nevertheless thrombi were also found in practically every vessel, large or small, artery or vein.

The findings regarding *time of occurrence* did not always conform to orthodox conceptions: on the 10th to 14th postoperative day following sudden movement, for surgical cases; after weeks or months of recumbency, for medical cases. Among surgical cases, thrombosis and embolism were found to occur anywhere from the time of operation itself to 4 months. One patient had been up and around 4 days when a fatal embolism occurred; another was just entering a cab to go home. Among medical cases, the range ran from the first few minutes following admission, while a history was still being taken, to 1 year. Whereas medical cases on the whole tended to occur later, many of them nevertheless occurred within 1 to 3 weeks

following admission, a period comparable to the orthodox post-operative period among surgical cases.

In more than one-third of the cases, thrombi were located in more than one vessel or organ (for example, femoral vein, adrenal artery and pulmonary artery). In other cases, multiple thrombi were located in the same vessel or organ, particularly the lung. Often these multiple thrombi showed various ages or stages of organization. Hence this series confirms the opinion of Belt,⁴ Barnes,² and others that thrombosis (and embolism) is most often not a single occurrence but rather a series of occurrences over a period of hours, days or months.

In its effect on the patient, thrombosis extended from a mere incidental postmortem finding through all the stages of morbidity to sudden death. As a cause of sudden postoperative death it has long been recognized, and many efforts have been made to prevent it. As a more frequent cause of morbidity, it has been rather neglected. In this series, for every case in which death was immediately due to thrombosis, there were approximately 3 cases in which it was not. In approximately half of all the surgical cases, thrombosis was a mere incidental finding. No case of thrombosis in the operative site, except dural sinus thrombosis, was of any local consequence, and none was followed by embolism.

The difficulty of classifying patients unequivocally as medical, surgical, traumatic, and so forth, is equalled by the difficulty of classifying thrombosis as simply an incidental finding, as a cause of morbidity, or as a cause of death. This difficulty is frequently encountered in surgical cases dying slowly in coma from pneumonia, hemorrhage, or peritonitis, but with large potentially fatal thrombi, and in medical cases dying suddenly from thrombosis but with potentially fatal cancer, uremia, or peritonitis.

Contradictions. The many contradictions and inconsistencies encountered throughout this series provided a barrier to the formulation of any scheme for the prevention of thrombosis applicable to all cases. Elderly patients with a clinical history of carditis, severe sclerosis, prolonged recumbency, an abdominal operation with subsequent infection and anemia would reveal at postmortem advanced cardiac degeneration, marked pulmonary sclerosis, an aorta covered with atheromatous ulcers throughout its length and down into the femorals—in fact all the supposedly thrombogenic factors, clinical and pathologic—but no thrombus. On the other hand, thrombi have been unexpectedly found in young non-surgical patients in the apparent absence of most of these factors. While such paradoxical illustrations are fairly commonplace, a number of other inconsistencies and contradictions encountered here warrant brief mention:

1. *Length of Recumbency.* It seemed reasonable to expect that among elderly patients, particularly those with cardiovascular dis-

ease, a prolonged period of recumbency should result in changes conducive to thrombosis. As the number and the hospitalization of elderly patients continue to increase, the study of geriatrics receives wider recognition. Hypostatic pneumonia represents one familiar possibility to be considered in the management of such patients. Recently the effects of prolonged recumbency in elderly persons—at least those effects susceptible of being measured and evaluated—were reported by Laplace and Nicholson.¹⁴ While 10 of their 17 fatalities were laid to recumbency, in no case did it take the form of thrombosis. Nevertheless the effects of recumbency which they considered to be of primary importance, namely, those concerning the blood-vascular system, are the very ones believed to be decidedly thrombogenic in this series of cases. These include: 1, a sharp decrease in the number and extent of skeletal muscle contractions; 2, decreased voluntary and heart muscle tonus; 3, accumulation of blood in venous capillaries with diminished volume in large vessels; 4, hypostatic congestion in both systemic and pulmonary circulations; 5, a drop in venous and arterial blood pressure. They believed the resultant state of relative circulatory insufficiency to be closely analogous to shock before the stage of vasomotor collapse.

While the changes consequent upon recumbency undoubtedly play an important rôle, what came as a surprise in this series was the briefness of the period of the recumbency. Many medical cases died within the first 3 weeks of hospitalization with its resultant abrupt slowing of all vital activities, a period corresponding to the usual period in postoperative embolism. It would seem that the abruptness of recumbency—with its demand for major adjustments—rather than its duration played the more important rôle. Laplace and Nicholson designated the critical period of recumbency to begin as early as the 2d week and to extend through the 4th week; if the patient survived this period, he had little to fear from additional recumbency.

2. *Nature of Surgical Procedures.* Again it seemed reasonable to expect that subjecting elderly patients to long operations under deep anesthesia with resultant loss of blood and body fluids, drop in pressure and immobility should produce a combination very conducive to thrombosis. Undoubtedly it does. While such combinations did occur, the relatively short and simple nature of many of the operations was unexpected. Because half of them were for cancer, and because a majority of cancer patients arrived here in advanced stages, many of the operations proved to be merely brief explorations with the thrombogenic factors listed above present in only slight degree. Of the 198 operations, 108 were laparotomies. There were 22 prostatectomies (16 transurethral, 6 suprapubic). Relatively few spinal anesthetics were given. In the majority of cases cyclopropane was used.

3. *Age of Patients.* Whereas the majority of patients were between 40 and 70 years of age, one-seventh of them (91) were under age 30. The thrombi found in these early cases did not represent merely incidental findings; they exhibited the same range from incidental finding to cause of sudden death as did the thrombi in the older cases. Many of them were associated with inflammatory diseases of the heart as the older cases were associated with degenerative diseases. Rheumatic heart disease played an important part. For example, Case 30:132 was a 13-year-old boy hospitalized 2 months with rheumatic heart disease; he died suddenly and unexpectedly while talking to the nurse, with thrombosis of one branch of the pulmonary artery. The youngest case of pulmonary embolism occurred in an infant 8½ months old, Case 35:275, hospitalized only 6 days and exposed to no more hazardous treatment than bilateral myringotomy.

Because of its contradictory and deceptive clinical behavior, accurate diagnoses at times proved very difficult or even impossible. The fact that major pulmonary thrombosis may form during a state of coma from some other condition such as peritonitis or uremia, and so mask or fail to provoke any sudden clinical episode, indicates one type of difficulty. Another familiar type is illustrated by the following 2 cases: Case 37:136 was a woman aged 61 who died suddenly following movement on the 19th day after cholecystectomy. Though clinically it appeared to be typical pulmonary embolism, none was found at autopsy; the death was cardiac. Case 36:101 was a man being treated conservatively for gall bladder disease; on his 16th day of recumbency he turned on his side and suddenly died. At autopsy, while other lesions were also present, there was a gross pulmonary thrombosis.

It is not essential for the consideration of thrombosis as primarily a medical problem to present a detailed description of all its principal types. They nearly all lend support to this consideration. However, as they do so in slightly different fashion, a brief description will be given of four of them—pulmonary, cardiac, coronary, and inguinal.

Pulmonary Thrombi (and Emboli).—It can be seen from Table 2 that both in frequency of occurrence and in seriousness of effect pulmonary thrombi (and emboli) rank first in this series, far ahead of coronary and cerebral thrombi, the other potentially fatal types most frequently found. Barnes² in a recent article on pulmonary emboli estimated that over 3,000,000 persons now living in the United States would ultimately die of this condition, and he regretted the failure of vital statistics to indicate its true magnitude. Jackson¹³ believes that many acute attacks now being diagnosed as coronary thrombosis are not coronary thrombosis at all, but actually thrombosis (or embolism) of the pulmonary artery. This series of cases tends to substantiate the conclusions of both men. A striking illus-

tration can be provided by Case 37:300: this woman, aged 62, a cardiac patient without previous hospitalization, suddenly dropped dead in a few minutes after admission, while a brief history was being taken preparatory to assigning her to the proper service. Postmortem disclosed a massive fresh bilateral pulmonary thrombus.

The above case also may be used in directing attention toward two of the prominent traits of pulmonary thrombosis in this series: 1, its tendency to occur more often among strictly medical patients; and, 2, the brief period of hospitalization (or recumbency), if any, necessary for its formation in medical cases. As shown in Table 2, two-thirds of this group were strictly medical patients. Many of the ordinary medical cases occurred within 1 to 4 weeks of admission, the critical period of recumbency in the development of this condition.

TABLE 2.—PULMONARY THROMBOSIS AND EMBOLISM.

	Medical cases. 226.	Surgical cases. 98.	Miscellaneous cases. 17.	Total cases. 341.
Size:				
Gross	142	64	14	220
Microscopic	84	34	3	121
Alone, or with other thrombi:				
Alone	125	61	9	195
With cardiac thrombi	49	7	..	56
With coronary thrombi	10	1	..	11
With inguinal thrombi	21	7	4	32
With any other thrombi	69	30	4	103
Associated diseases:				
Cardiac: primary	106	2	..	108
secondary	61	55	8	124
Cancer	58	53	1	112
Effect:				
Incidental finding only	57	29	3	89
Contributory	80	38	10	128
Fatal: with sudden death	50	18	3	71
without sudden death	39	13	1	53

Table 2 brings out the preponderance of cardiac patients among the medical cases. In almost half of the medical cases it was the primary ailment, and in half of the remainder it was an important secondary ailment; 49 medical cases also showed cardiac (mural) thrombi, and 10 coronary thrombi. Unfortunately, no tabulation was made of cases showing marked coronary disease or occlusion without actual thrombi; otherwise the close relationship would have been more evident.

The only other condition occurring often enough to warrant inclusion in Table 2 was cancer. Among the 31 surgical cases where death was directly attributable to thrombosis (or embolism), cancer was present in 16 cases. Non-cardiac, non-cancer cases accordingly occurred only rarely.

Two additional characteristics of these thrombi deserve mention. First, non-fatal pulmonary thrombosis, with or without clinical or pathologic significance, outnumbers (217 to 124) the fatal form, and

indicates its numerically greater rôle in causing morbidity of various degrees instead of immediate death. As only actually demonstrated thrombi were used in this series as a basis for the statistics, cases with pulmonary infarct but no discernible thrombus were not included; otherwise its rôle in morbidity would assume greater proportion. *Second*, among cases where differentiation could be made with assurance, pulmonary thrombosis outnumbered pulmonary embolism particularly in the non-fatal cases.

Cardiac Thrombi.—In numbers, if not in fatal potentialities, uninfected cardiac or mural thrombi of various forms came second, as shown in Table 3. To the belief that thrombosis is primarily a medical problem, two features in particular lend support: 1, the large proportion (117 out of 140) of strictly medical cases; and, 2, the even larger proportion of patients (126 out of 140) with primary or secondary heart disease of one type or another. The comparatively few cases of cancer are striking in view of its much larger proportion in the other groups.

Certain of the findings in this group duplicated findings by Harvey and Levine⁹ in a study of Boston autopsies between 1913 and 1929. They found 111 uninfected thrombi among 2091 posts, an incidence of 5.3%; here 140 were found, an incidence of 5.4%. In their series 66% were males; here 58%. In both series, the four chambers were involved in the same order of frequency: right auricle, left ventricle, left auricle, right ventricle; the auricular appendages and the ventricular apices were the commonest sites. They concluded that ventricular damage (infarction) subsequent to coronary disease, particularly occlusion, and stasis from improper functioning of the auricles, particularly fibrillation, were the two most frequent mechanisms for the formation of cardiac thrombi. Myocardial fibrosis appeared as a very common underlying condition in this series. While the majority of cases in both series occurred after age 40, where degenerative heart disease prevails, in our series 14 cases occurred before age 30, 7 of them with rheumatic heart disease. Among the entire group of 140 cases, the ages ranged from 11 months to 97 years.

The effect of mural thrombosis on the patient has not been included in Table 3 because it proved too difficult to evaluate with reasonable assurance, mural thrombi frequently forming only one link in a chain of lesions. To separate their individual effect from the total effect is practically impossible. While fatal cases have been reported, in no instance in this series was mural thrombosis regarded as the immediate cause of death. Undoubtedly it provided the origin of several instances of fatal embolism elsewhere.

Coronary Thrombi (see Table 4). It seems superfluous to use coronary thrombosis in support of a conception of thrombosis as a medical problem, since it occurs predominantly among medical (cardiac) patients. Whereas recognition and understanding of the

nature of thrombosis in general have been due largely to pathologists (beginning with Virchow²² in 1846-56 and including Welch²⁴ and Aschoff¹), recognition and interest in coronary thromboses have been due almost solely to clinicians (beginning with Herrick¹¹ in

TABLE 3.—CARDIAC (MURAL) THROMBOSIS.

	Medical cases.	Surgical cases.	Miscellaneous cases.	Total cases.
Number of cases:	117.	23.	0.	140.
Sex:				
Male	81	16	..	97
Female	36	7	..	43
Size:				
Gross	103	18	..	121
Microscopic	14	5	..	19
Number of chambers involved:				
Single	78	19	..	97
Multiple	39	4	..	43
Alone or with other thrombi:				
Alone	38	10	..	48
With pulmonary thrombi	49	7	..	56
With coronary thrombi	13	3	..	16
With inguinal thrombi	5	3	..	8
With any other thrombi	32	7	..	39
Associated diseases:				
Cardiac: primary	90	5	..	95
secondary	18	13	..	31
Cancer	7	5	..	12

TABLE 4.—CORONARY THROMBOSIS.

	Medical cases.	Surgical cases.	Miscellaneous cases.	Total cases.
Number of cases:	34.	6.	0.	40.
Sex:				
Male	28	6	..	34
Female	6	0	..	6
Size:				
Gross	16	2	..	18
Microscopic	18	4	..	22
Associated lesions:				
Infarct	20	4	..	24
Cardiac thrombus	13	3	..	16
Pericarditis	14	2	..	16
Rupture	2	2
Aneurysm	4	1	..	5
Pulmonary thrombus	10	1	..	11
Other thrombus	11	11
Number of episodes:				
None	17	3	..	20
Single	2	2	..	4
Multiple	15	1	..	16
Effect:				
Incidental finding only	12	2	..	14
Contributory	14	3	..	17
Fatal with sudden death	8	1	..	9

1912 and including Riesman,²¹ Levine,¹⁵ Middleton,¹⁷ and Willis.²⁶ By its nature and location it combines elements both of heart disease and of thrombosis. It is accountable directly and indirectly for a multitude of lesions in both categories. Case 37:49 furnished a concrete illustration of the wide extent of its accountability: This

man, aged 55, gave a history of coronary attacks over a period of 26 months. He died 12 days following admission. At postmortem there were found a large, fairly recent thrombus occluding the anterior descending branch of the left coronary, an older calcified thrombus in one of its larger branches, and microscopic thrombi in numerous small branches; mural thrombi of various ages in three chambers; multiple areas of old and recent myocardial infarction; impacted emboli in the pulmonary arteries, with smaller propagating thrombi beyond them and with multiple areas of old and recent pulmonary infarction.

Among the common heart lesions found at autopsy, coronary thrombosis ranked eighth, far behind chronic fibrous myocarditis and coronary sclerosis. Heart lesions among the 2613 postmortems occurred very frequently, reflecting the constantly large proportion of heart patients among the hospital population. However, the majority of such patients were of the rheumatic, chronic degenerative, or congestive heart failure type, more conducive to mural or pulmonary thrombosis, and not of the anginal type, more related to coronary thrombosis. Like cerebral thrombosis, it frequently occurs as a primary ailment, during activity, outside the hospital, and may not result in hospitalization. Mural and pulmonary thromboses in this series were shown to occur as secondary complications following hospitalization or recumbency. Like hypostatic pneumonia, they represent hazards of hospitalization; they are the results of recumbency. Coronary thrombosis, on the other hand, is a cause of recumbency. In severity of effect, it produced only 9 fatalities compared with the 78 fatalities produced by massive pulmonary thrombosis or embolism. This lends support to the belief of Jackson¹³ and others that many attacks diagnosed as coronary thrombosis without autopsy confirmation are in reality examples of pulmonary thrombosis.

Among the principal types of thrombosis, coronary thrombosis ranked sixth, and might have fallen to seventh had there been more brain examinations. It must be stated, however, that only actual thrombi, in the exact pathologic meaning of that term, were included. Occlusion produced by methods other than thrombosis (sclerosis and possibly spasm) were excluded, as were cases of myocardial infarction (two to three times as frequent as thrombosis) wherein no thrombus was found. Half of the cases were merely of microscopic size. Yet microscopic thrombi in this organ are as important as in the brain, since Blumgart⁵ has recently demonstrated the damaging effects of anoxia in heart muscle of only a few minutes' duration.

Apart from its low incidence, a number of miscellaneous findings might be mentioned for their general interest. Sex: males outnumbered females 5 to 1. This ratio was obtained also in another disease in this series of 2613 postmortems, namely cancer of the

lung, wherein the culpability of tobacco has also been raised. In White's²⁵ series of 21 clinical cases of coronary thrombosis under age 40, all used tobacco. *Age*: although the majority of cases fell between the ages of 50 and 70, there were 4 young cases (ages 8, 14, 17 and 25), all of whom showed rheumatic stigmata. *Occupation*: that coronary thrombosis is not confined to a wealthy, white-collared, worried clientele, such as have furnished the material in the reports of numerous clinicians, is shown by the occupations and financial status of the patients comprising this series. Most of them were farmers or laborers with only 3 non-manual workers among the males. Of the 40, 37 were ward patients. *Surgical cases*: though it was necessary to classify 6 cases as surgical, all of them were actually cardiac patients with a superimposed surgical emergency, such as acute appendicitis or acute urinary retention. *Canalization*: 5 cases showed restoration of flow through recanalization, a method somewhat neglected or forgotten in the search for adequate collateral flow.

TABLE 5.—INGUINAL (ILEO-FEMORAL) THROMBOSIS.

	Medical cases.	Surgical cases.	Miscellaneous cases.	Total cases.
	33.	13.	6.	52.
Vessel:				
Artery	7	1	..	8
Vein	24	11	6	41
Both	2	1	..	3
Side:				
Right	12	4	1	17
Left	12	8	3	23
Both	9	1	2	12
Number infected	15	8	2	25
Associated diseases:				
Cardiac: primary	9	9
secondary	14	8	3	25
Cancer	14	11	1	26
Effect:				
Incidental finding only	11	8	2	21
Contributory	16	2	1	19
With fatal embolism	6	3	3	12

Inguinal Thrombi (see Table 5). Thrombi in these vessels (ileo-femoral arteries and veins) were found less frequently than thrombi in the pelvic veins (74 cases) or in the aorta (56 cases). There were 52 cases divided almost evenly as to sex, with 27 males and 25 females. The inguinal region, embracing both iliac and femoral, is one wherein structural or mechanical handicaps combine under certain provocations to exert a powerful thrombogenic influence. Any list of such handicaps would naturally include the following: the compression of both artery and vein under Poupart's ligament; compression of the iliac vein under the artery; compression from regional abnormalities (in this series enlarged lymph nodes due to infection, cancer, metastases, aleukemia, abscess, and dissecting hematoma); abdominal or pelvic distention from fluid or gas; the venous valves; the entering angle of contributory veins; supine

position in bed with failure to relax groin by bending knee; immobility, venous stasis, decreased muscle and vessel tonus, distance from the heart. Like the pelvic veins, these vessels lie close to the divide between the portal vein drainage and the vena cava drainage, and consequently are susceptible to the effects, if any, of a reflux of portal blood into the systemic veins (Havlicek's¹⁰ theory of thrombogenesis). The comparative freedom of the axillary region from such handicaps is indicated by the presence of only 5 cases with thrombosis in that region, all apparently provoked by some unusual impediment to venous return (cancer of lung, axillary metastases, large pleural effusions).

This region, accordingly, in the size and importance of its vessels, and in its vulnerability to a multitude of structural handicaps, appears to offer an ideal site for the formation of dangerous thrombi whenever the imposition of an additional hazard, as an operation, a fracture, or a birth, activates these potential handicaps. Yet, as Table 5 shows, such additional provocation need not be required: a majority of these thrombi were found in medical patients subjected only to recumbency.

Ten of the patients placed correctly in the medical group illustrate nevertheless how easily and erroneously at times surgery can be held accountable for the thrombus. Seven of them had cancers thought to be too far advanced for surgery, 2 had cancers being treated with Roentgen ray instead of surgery, and 1 had a goiter, causing too great a risk for surgery. Similar cases, though with thrombi in different sites, were encountered wherein surgery was not undertaken because of the advanced state of the disease (generally cancer), the poor risk, or because other treatment was substituted. Other cases were encountered wherein surgery had been postponed, supposedly merely temporarily, because of elevated temperature, sore throat, or irrelevant personal reasons. Yet in all these cases, had the desired or contemplated surgery taken place, it would ordinarily have been held accountable for the thrombosis found at postmortem; it would have been necessarily classified as a surgical case in this series.

Among the medical cases the period of recumbency frequently lasted less than 3 weeks. Among the surgical cases the postoperative period of recumbency never was longer than 19 days, and generally was 11 to 14 days. However, 1 case dying on the day of operation for brain tumor, with a large incidental inguinal thrombosis at postmortem, brings out the need of considering the pre-operative period also. Case 34:197 indicates that even recumbency is not required when underlying factors are sufficiently strong: in this patient, a man of 48, the thrombus first made itself manifest very abruptly while he was bent over in a field picking cucumbers; the process had been set in motion by a metastasis from an unsuspected cancer of the rectum. Among fracture cases on the ortho-

pedic service, customarily subjected to the longest periods of recumbency and immobility, only 4 cases of inguinal thrombosis were found.

Summarizing the rather inconsistent influence of recumbency in this area, it was found that 1, inguinal thrombosis occurred most often among strictly medical cases; 2, it occurred rarely among fracture cases subjected to the longest periods of recumbency; and 3, it occurred frequently within a comparatively short time, seemingly instigated more by the shock and abruptness of recumbency than its prolongation.

The potentialities of large inguinal thrombi in cases where death was due to other causes can best be indicated by citing a typical instance: Case 33:248 was a 65-year-old male who died of cancer and heart disease 30 days following the application of a double hip spica (fracture due to cancer metastases). At postmortem, the left ileo-femoral vein was completely thrombosed from a point too far below Poupart's ligament to be reached by probing up to the origin of the inferior vena cava. There had been no swelling of the leg, no clinical manifestation and no embolus. It was merely an incidental postmortem finding.

Altogether 13 such cases were found of large potentially dangerous inguinal thrombosis. They make one wonder what would happen if the patient had not died of an intervening pneumonia, uremia, peritonitis, cancer, or heart disease. They make evaluation of the effect of these thrombi difficult and raise objection against classifying them as merely incidental findings. Though all of the inguinal thrombi were large, one extending from the level of the renal artery to the popliteal fossa, only 12 of them gave rise to fatal embolism.

Discussion. Virchow²² between 1846 and 1856 evolved a conception of thrombosis, largely mechanical, that is accepted today. He declared the process to be dependent upon three conditions: 1, alteration (slowing) of the blood current; 2, alteration (damage generally from infection or degeneration) in the vessel wall; 3, alteration (chemical and physical) in the blood content. Since his time other students of the problem have furnished additional details or refinements of these three fundamental conditions. Zahn²⁷ called attention not only to the architecture of a thrombus, but to the necessity for a flowing stream; von Recklinghausen²⁰ to the whirling or eddying current. Welch²⁴ repeated many of the earlier experiments, particularly those of Eberth and Schimmelbusch,⁸ emphasizing the combination of a slowed circulation and a damaged intima. Howell¹² added heparin, a constituent of the blood formed in the liver. Dietrich,⁷ studying war-time thrombi, emphasized infection. Aschoff,¹ studying peace-time thrombi, emphasized stasis. Havlicek¹⁰ believes a reflux of toxin-laden blood from the portal system into the caval system leads to agglutination and thrombosis. Peterson¹⁹ believes the weather exerts a marked thrombogenetic influence; that certain meteorologic pressor episodes produce a fall in

blood pressure, a sticky endothelium, an increase in fibrinogen, and a relatively acid organic status. Murray and Best¹⁸ and their co-workers are currently administering refined and concentrated heparin to human beings and determining what protection it affords following extensive surgical procedures.

The cases in this series are indicative not only of the increased incidence of thrombosis which has taken place largely since the World War, but also of its preponderance among strictly medical patients and of its more frequent rôle as a cause of morbidity than of death. Its increase has been attributed to a number of circumstances, particularly: 1, lengthening of the average life expectancy; 2, consequent increase in number and longer survival of cardiac patients; 3, increase in the hospitalization of patients, and in general, earlier and more widespread resort to recumbency, to the practice of "going to bed," with less provocation than in hardier days; 4, larger volume of surgery; 5, greater use, especially among the Germans, of intravenous therapy and diuretics. Thrombosis should be placed besides pneumonia as one of the hazards of hospitalization. Of the 648 cases in this series, with the exception of 11 coronary cases, only 7 entered here because of thrombosis.

Analysis of the individual cases in this series indicates that thrombosis is a product of variables. In any 2 patients with thrombosis the factors entering into the process may vary widely in number, in individual potency, and in the manner in which they are combined. Again, in 2 patients of the same age and sex, with practically identical alterations in two of the fundamental conditions—for example, vessel wall (atheromata) and blood current (stasis)—with the same primary disease, and subjected to the same medical management, thrombosis may develop in one but not in the other. The antithrombotic (heparin?) composition of the blood content—the third fundamental—has been sufficient to provide protection in one case, but not in the other. It is a matter of degree as well as number of factors. Such variability increases the difficulty of developing any formula for prevention which could be applied in all cases.

This series emphasizes the importance of the underlying or dormant medical factors, not only among the medical patients but also among the surgical, obstetric and traumatic patients. When such factors are present in adequate degree the shock of a superimposed operation, fracture, or childbirth, is not essential. Abrupt recumbency for a period of only a few days or weeks is capable of setting the dormant thrombogenetic factors into motion.

Among medical factors, a decompensated cardiac condition overshadows all others. Cardiac patients of the anginal type, without decompensation, are prone to develop coronary thrombosis. To them recumbency is no hazard. Cardiac patients without angina, but with decompensation, are prone to develop other forms of thrombosis—mural, pulmonary, inguinal, and pelvic. To them

recumbency is a hazard. They need not be elderly patients with progressive degeneration of the cardiovascular equipment, although such patients constituted the majority here. They may be young patients generally with rheumatic or bacterial inflammation. It is the condition of decompensation, not whether its cause is degeneration or inflammation, nor the age of the patient, which is important.

Prevention. Many practical measures to prevent thrombosis have been recommended, mainly by surgeons attempting to avoid postoperative embolism. For a list of such measures and a discussion of their merits, two recent publications are helpful: An article on Pulmonary Embolism, by Arlie Barnes,² and a chapter on Thrombosis, by John Homans.¹⁶ According to Homans, most measures are aimed at three objectives: to keep the fluid content normal, to prevent a rise in intraabdominal pressure, and to invigorate the venous return from the legs. He believes that if everyone confined to bed under conditions which threaten thrombosis could live with the foot of the bed elevated and could be protected from increased intraabdominal pressure, thrombosis and embolism would never occur (granting at the same time the limited application of such methods because of other dangers).

Thrombosis, however, does not arise from any single cause, and there is no specific preventive. Being a product of variables, no constant formula for prevention can be laid down. In this series, it appears most frequently as the consequence of a chain of dormant medical factors (such as an impaired heart plus a local handicap plus deficient anticoagulant quality of blood) activated by the imposition of some shock (operation, trauma, pregnancy, recumbency). The links in the chain varied widely in number and in individual potency. The predominant medical factor, however, was an impaired heart (regardless of age), and the predominant activating shock was simple recumbency among strictly medical patients. Consequently, whatever additional measures of prevention may be suggested by this series, they apply to these two conditions.

1. *Impaired Heart.* Inasmuch as thrombosis is an abnormality of the vascular system (heart, vessels, blood), maintenance or restoration of the normal structure and functioning of this system is the chief objective. Avoidance of, or protection against, outside interference with its normal function must likewise be included. Typical illustration of outside interference is furnished by encroaching tumors, by compression under Poupert's ligament, by the pressure of large volumes of fluid in the abdominal or pleural cavities. Cardiac competency is the greatest single defense against thrombosis, and its lack the greatest single danger. Decompensation—for reasons obviously more serious than the possibility of thrombosis—should be corrected wherever possible. In so doing many conditions conducive to thrombosis, which may exist independently, however, as well as secondary to decompensation, will be overcome.

Typical illustration of such conditions is furnished by congestion or stasis in either the pulmonic or the systemic circulation (leg and pelvis particularly), by auricular fibrillation, by reduction of fluid within the vascular system (dehydration), by enfeebled blood current.

2. *Recumbency*. Under certain circumstances the benefits of recumbency are also accompanied by a certain degree of risk or hazard. The circumstances have to do chiefly with cardiac impairment, regardless of age, with or without decompensation, but excluding the anginal type. The risks include: 1, a condition of general circulatory deterioration described by Laplace and Nicholson¹⁴ as analogous to shock; 2, hypostatic bronchopneumonia, and, 3, thrombosis. They arise apparently from the abruptness of the change, as the critical period is relatively short, covering only the first 2 or 3 weeks. They can be reduced by any measures undertaken to make the transition to a complete bedridden status a gradual rather than a sudden process, both in time and in methods. These measures must be varied according to the nature and degree of the patient's illness, but in general as much mobility of the patient should be retained or provided as is compatible with his condition.

A certain amount of regular or daily mobility provides the best single protection against the risks of recumbency. Homans, advocating short confinements after abdominal operations, believes convalescence is shortened and vigor more quickly regained when the patient has been made to get out of bed very early, if only for a few minutes daily. For strictly medical patients the risks of recumbency are reduced in proportion to the degree of mobility retained during the relatively short critical period of transition to a bedridden status.

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CORONARY THROMBOSIS AMONG WOMEN.

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LITTLE doubt exists that coronary thrombosis occurs more frequently today than ever before, and numerous opinions have been expressed in explanation of this phenomenon. Prominent among them is the assertion that a better and more widespread understanding of the disease has greatly increased the accuracy of diagnosis and that the increased incidence, therefore, is apparent rather than real. It is true that the medical profession at large has improved the accuracy of diagnosis but this fact does not wholly satisfy the presumption that the incidence of coronary thrombosis has not increased, as careful analyses of postmortem material of two decades ago reveal relatively few cases of coronary thrombosis as compared to the cases that are observed today.

Another frequently aired opinion emphasizes the influence of the stresses and strains of modern life, the worries contingent on financial catastrophies and the ever-increasing uncertainties prevailing in the business world of today. There seems to be little doubt that these stresses are participating factors, but again the question is not completely answered.

Likewise, the influences of heredity have been mentioned as noteworthy factors in the increasing incidence of coronary thrombosis. This belief has been based on the assumption that the United States has reached the age where the adverse influences of heredity, so far as the cardiovascular system is concerned, are becoming evident owing to the conspiring influences of the modern environment. While the influences of heredity cannot be denied, the data on the subject are so inadequate that this thesis cannot be established as a fact.

The solution of the problem seems to depend on the solution of the cause or causes of atherosclerosis, and it appears at this time that the answer may be supplied through the medium of biochemistry.

The reasons for our interest in the subject of coronary thrombosis among women are dependent largely on certain data disclosed in a previous investigation by one of us.³ This study, which comprised 370 cases of coronary thrombosis, was based only on the selection of cases in which complete data were available. It disclosed that

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there was a great discrepancy in the incidence according to sex. There was a marked predominance among men; the ratio of men to women was 7 to 1. Furthermore, it was shown that coronary thrombosis occurred considerably later in life among women than it did among men; in fact, it occurred on an average of 6 years later among women. It, therefore, seemed desirable to study carefully a larger group of women who had coronary thrombosis, in order to determine, if possible, any other striking differences in the manifestations of the disease in the two sexes.

Levy and Boas² recently reported a study of 169 women who had coronary disease. Their patients were not selected exclusively on the basis of coronary thrombosis but on criteria that warranted the diagnosis of coronary disease. Their conclusions, which are substantiated only in part by this study, included the following deductions: 1, Coronary disease is more common among men than among women, and in all but 7.7% of the cases either hypertension or diabetes mellitus occurred; and, 2, coronary disease occurs infrequently among women under the age of 50, unless it is associated with hypertension or diabetes mellitus.

Material. One hundred consecutive women who had coronary thrombosis form the basis for this study. In 35 cases the occlusion occurred while the patients were under observation at The Mayo Clinic. Sixteen patients were observed within a month following the occlusion, 24 within 6 months, 7 within a year, 7 within 18 months and 7 after 2 years or more. In 4 cases, it was impossible to determine accurately the time that coronary thrombosis occurred. In cases in which the patients were not observed during the time of acute coronary closure, characteristic histories, typical electrocardiographic findings or demonstration of the infarct at necropsy were convincing evidence of its occurrence.

Age Incidence. Only 8 patients were less than 50 years of age at the time the thrombosis occurred; 2 were in the fourth and 6 were in the fifth decades of life respectively. The youngest patient was aged 30, the oldest 85, and the average age for the group was 63. The average age for males in the previous study³ was 57.3 years. Eighty-nine per cent of the patients were in the sixth, seventh or eighth decade of life, while in the previous study 79% of the men were in the same age periods. Three women were between the ages of 80 and 89. These data clearly demonstrate the tendency for coronary thrombosis to occur later in life among women than among men.

Mortality. In 54 cases the patients were dead at the conclusion of this study and in all but 9 of these cases death was directly attributable to the heart. In 32 cases death occurred soon after coronary occlusion and in 13 cases later, as a result of ensuing congestive heart failure. In 4 cases the cause of death could not be determined; in 5 cases death resulted from diseases entirely unrelated to the heart. Forty-six patients were living at the conclusion of the study.

Recurrent Coronary Thrombosis. Seven patients suffered from recurrent coronary thrombosis. This incidence is considerably less than that noted in the previous study, which comprised both men and women. In that study, the incidence of recurrent episodes was found to be 19.7%.

In 6 cases, 2 attacks of coronary thrombosis occurred and 1 patient

survived 3 attacks. This patient is living and well, $7\frac{1}{2}$ years following the first occlusive episode and 4 years following the third; she is now 73 years of age. The intervals between the attacks ranged from 2 months to $7\frac{1}{2}$ years.

Another patient, who had 2 attacks of coronary thrombosis, is living and well. She is now 83 and had the last attack 4 months before this article was written. These 2 patients emphasize the remarkable tolerance and reparative powers of the heart to such severe disease which is observed from time to time even among aged persons.

Evidences of Heart Disease Preceding Coronary Thrombosis. In 78 cases subjective evidence of heart disease occurred before the onset of coronary thrombosis. The symptoms had been present from 2 months to 15 years. The most common symptom was dyspnea which was associated with accustomed effort; this occurred in 65 cases. The anginal syndrome occurred in 27 cases. Thirteen patients had had one episode of congestive heart failure; hypertensive heart disease was coexistent in every case in which congestive heart failure had occurred. Some overlapping of these symptoms obviously occurred. It is interesting and significant that only 22 patients experienced their first conclusive cardiac symptoms with the onset of coronary thrombosis.

Associated Conditions. We were greatly interested in the report of Levy and Boas, in which they said that hypertension and diabetes mellitus occurred in 92.3% of the cases. This incidence was considerably out of line with our clinical impressions.

In our series 66 patients were known to have had hypertension before the onset of coronary thrombosis and it is probable that the incidence actually was somewhat higher, owing to the fact that blood pressure at times fails to attain its former level after an attack of coronary occlusion.

Data regarding diabetes mellitus were available in all but 12 cases; in these cases death occurred very soon after the occlusive attack and before laboratory studies could be carried out. Only 11 patients had diabetes mellitus. It is, of course, true that the degree of atherosclerosis frequently is marked among diabetic patients and that coronary disease among them is common. Variations in the results of different groups of clinical material obviously occur and it, therefore, is important not to accord too much importance to certain incidental findings.

In 77 cases the ratios of height and weight were available; in 87% of these cases there were varying and definite degrees of obesity. In a previous publication, Goldsmith and Willius¹ presented data obtained in 300 cases of coronary thrombosis; these data showed that a tendency to overweight occurred among patients of all ages with the exception of men who were over 70. There seems to be no doubt that obesity is a very undesirable status in heart disease and of itself is capable of swinging the balance from cardiac competence to incompetence.

The rather frequent association of cholecystic disease and coronary disease has received considerable attention, and the association of cholecystic disease and obesity also has been noted. In this study 16 patients had proven disease of the gall bladder. Nine patients had been operated on elsewhere, prior to the onset of coronary thrombosis; 2 were operated on after recovery, and in the remaining 5 cases, cholecystographic study clearly revealed the condition.

The occurrence of other diseases, such as carcinoma, hyperthyroidism, syphilis, and so on was purely casual and merits only mention.

Situation of Infarcts. In 86 cases the situation of the infarct was determined by electrocardiographic study or by postmortem examination. In the remaining cases death occurred before electrocardiographic examination was possible, or else necropsy was not permitted. It is interesting to note

that in all necropsied cases in which the electrocardiographic prediction of the situation of the infarct was made the predictions were proved to be correct.

The infarcts involved the anterior portion of the left ventricle in 30 cases, the posterior portion in 50 cases, and both anterior and posterior portions in 6 cases (recent and old infarcts). These figures are different from those of the previous study,³ in which the anterior surface of the left ventricle was involved in 56.3% of cases and the posterior wall in 43.6%. We do not believe that these differences are significant, but feel that they represent only the differences that may be anticipated in the study and comparison of different groups of cases.

Duration of Life in Cases in Which Coronary Thrombosis Proved Fatal. In 45 cases, as previously stated, death was directly attributable to coronary thrombosis or its sequelæ. Nine patients lived less than 24 hours following the onset of the occlusive episode. Six patients lived less than a week, 8 less than a month and 9 less than 6 months. Six patients lived less than a year, 4 lived less than 2 years and only 3 lived more than 2 years. The average duration of life in cases in which the patients died of heart disease was 11 months.

Duration of Life in Cases in Which Coronary Thrombosis Did Not Prove Fatal. Information was available regarding the state of health of 43 patients. Three patients could not be traced. Twenty-eight patients were alive within a period of 5 years following coronary thrombosis, 12 were alive within a period of 5 to 10 years and 3 lived more than 10 years.

Eighteen patients reported their state of health as good, 5 said that they were well with the exception of occasional anginal seizures, 14 were only in fair health and 6 were in very poor health. The latter include patients who had severe recurrent anginal seizures, severe dyspnea, congestive heart failure or a cerebral vascular accident.

Summary. Only two striking differences were noted in coronary thrombosis among women, as compared with men. The first is its relative infrequency among women; the ratio of men to women approximates 7 to 1. The second striking difference is the tendency for the disease to occur later in life among women; the average age of women was 6 years greater than the average age of the men. The relatively late appearance in life is presented more vividly if one recalls the fact that, in this series of cases, coronary thrombosis was recorded in 89% of the cases in which women were between the ages of 50 and 80 years and in 79% of cases in which men were of the same age. It therefore appears justifiable to assume that women are less susceptible to the development of coronary thrombosis than are men, and that when it occurs among women, it tends to occur later in life.

The association of hypertension, diabetes mellitus, and other conditions appears only to bear a relationship compatible with the predominant age periods represented by the group of patients included in this study.

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tery and polyhydramnios. The estimated development of the baby was about 32 weeks *in utero*. The weight was 1510 gm. The abdomen of the baby was enlarged and showed signs of fluid and it was diagnosed as congenital ascites. The baby cried once after delivery and became cyanotic and died.



FIG. 1.—Postmortem photograph showing single lung.

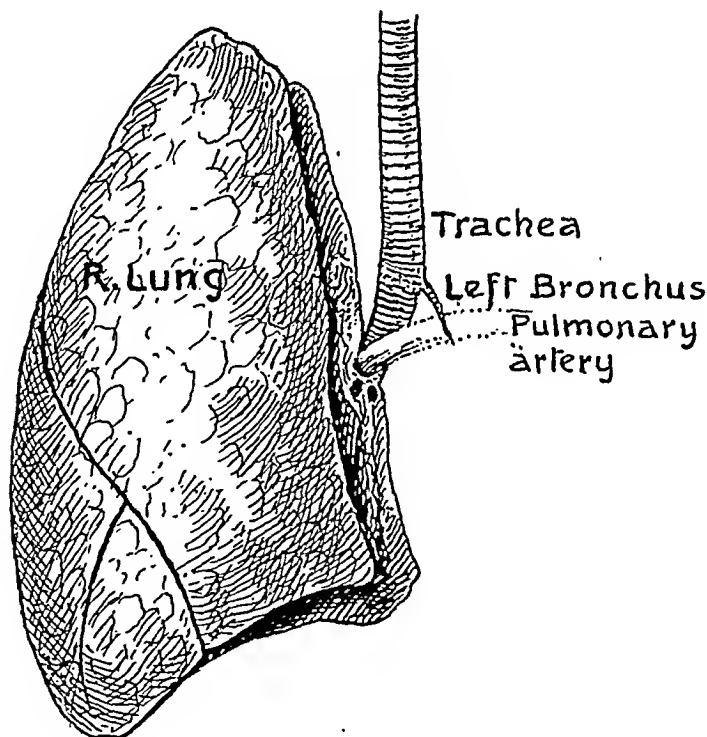


FIG. 2.—Drawing of arrangements at root of right lung.

Necropsy. The chest of this small baby is narrow and thin, the abdomen distended with fluid. There are about 100 cc. of clear yellowish fluid in the peritoneal cavity; the serous surfaces are smooth. The liver occupies

almost the whole upper part of the abdomen; the left lobe is larger than normal and there is also an azygos lobe on the posterior portion. There is no spleen; in the splenic area are a few spleen-like masses of tissue, purplish in color and a few millimeters in diameter. The intestine shows unusual rotation of the coils and the transverse colon is alongside the cecum and ascending portion.

The arrangement of the chest organs is abnormal. There is complete absence of left lung, the left pleural cavity being lined by thin parietal pleura and containing a small quantity of clear fluid. The heart is displaced to the left and occupies the space of the left pleural cavity (Fig. 1).

The right lung is connected with a normal right bronchus which is a continuation of the trachea. The lung tissue is soft and pale red and the size is larger than normal, the septa dividing the organ into four lobes.

The left bronchus is a rudimentary bud branching off from the trachea 2 mm. above the pulmonary artery and ending in a cul-de-sac; no lung tissue can be discovered (Fig. 2). This left bronchus is 8 mm. long; 1 mm. in diameter at the middle portion. The distal portion is small and tapers toward the end. The bud is soft and contains no cartilaginous rings.

The thymus is normal in shape and size. The pericardium is smooth and the cavity contains some fluid. The heart is normal in shape and size. The truncus arteriosus shows failure of division.

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A STUDY OF ORAL TYPHOID VACCINATION AS MEASURED BY BLOOD SERUM AGGLUTININS.

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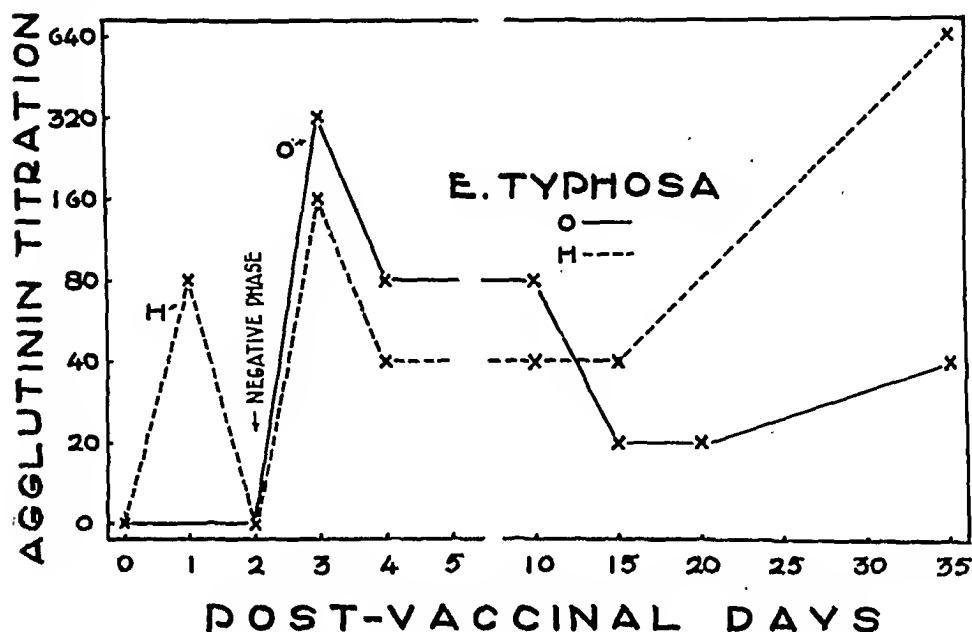
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In this study, 200 patients were vaccinated with mixed typhoid vaccine. One-half of the number were vaccinated by the subcutaneous method and the other half by the oral method. Blood serum agglutinins were determined at various intervals.

Numerous studies of oral vaccination with the typhoid and dysentery organisms have been made on various laboratory animals. According to Calmette,² Pasteur's work with chicken cholera (1880) first suggested the possibilities of oral vaccination. Wright⁴ was the first to attempt the oral method of immunization on human subjects. Besredka,¹ especially since the World War, has advocated his local immunity theory. This has given added impetus to the oral method of administering vaccine in the enteritides. The laboratory results have been varied and inconclusive. The first clinical application of the oral method of typhoid inoculation was in 1922.¹ Since that time over 500,000 cases of oral vaccination have been reported in the literature. The clinical results have been favorable and far more conclusive than the laboratory studies. Finder and

Simmons⁵ present an excellent survey of the literature on oral vaccination. Recently, Lacy and Cohen⁶ and Moor and Brown⁷ have made similar studies of the two methods of administering typhoid vaccine, as measured by the agglutinin titration of the blood sera in human subjects. The latter used the same vaccine as reported in the present study.



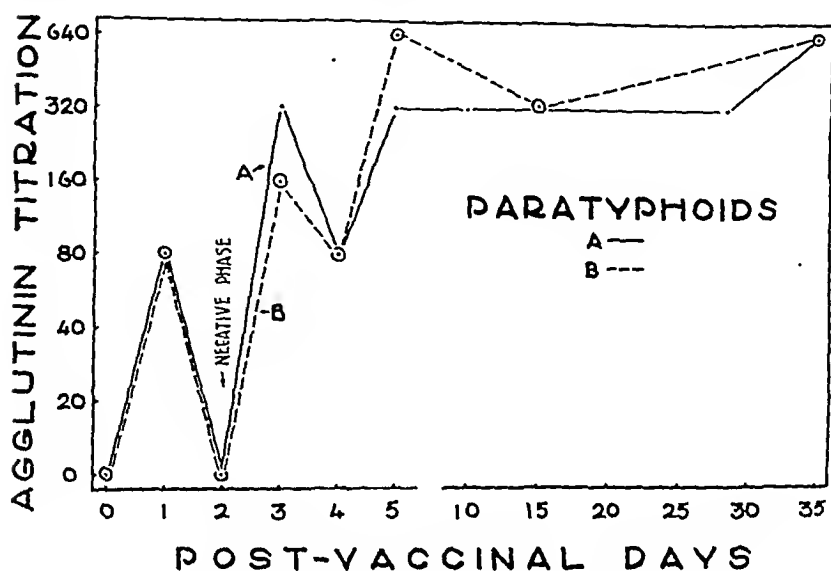
GRAPH 1.—Diagram showing the postvaccinal agglutinin changes in an individual following oral vaccine. This shows the manifestation, the induction phase and fluctuation of agglutinins of the "O" and "H" fractions of *E. typhosa*.

Methods. The oral and subcutaneous cases were unselected from a large group vaccinated during the Ohio River Valley Flood of 1937. The latter were given the mixed typhoid antigen subcutaneously in the usual series of 3 injections, each at an interval of 3 to 7 days. The agglutinins were then titrated 5 to 8 weeks following the completion of the vaccine injection.

Prior to administration of the oral vaccine, a history was obtained of previous vaccination, typhoid disease, or dysentery. A pre-vaccinal agglutinin titration was made. Following the oral vaccine, the agglutinins were again determined at 60 hours, 5 weeks and 6 months. Daily titers were determined on a number of the oral group, to determine the interval of agglutinin manifestation, the induction and the negative phase (which is prolonged by menstruation), together with the increase and fluctuation of the type specific agglutinins (Graphs 1 and 2).

The blood serum agglutinins were determined according to the method of Welch and Stuart.¹⁰ This method was used because of its expediency and the comparable results with the macroscopic test tube method. Controls were made using normal saline with each series of the bacterial suspension, in order to avoid spontaneous agglutination. Agglutinin titers were made for both the somatic ("O") and the flagellar ("H") fractions of the *E. typhosa* (*B. typhosum*) antigens and the mixed antigen of *S. paratyphi* (*Paratyphoid* α) and *S. schottmülleri* (*Paratyphoid* β). Dilutions ranged from 1 to 20 to 1 to 2580. The higher dilutions are only gross approximations.

The oral antigen used in this study was Typhoral—mixed.* A capsule of bile salts (gr. $\frac{3}{4}$) was administered 1 hour and 45 minutes before breakfast. The first capsule of antigen† was given 45 minutes later. The second and third capsules were given on successive days (without bile salts) 1 hour before breakfast. Thus, the oral vaccination is completed in 3 days. If optimal results are to be obtained, particular care must be taken in following this procedure of administering the vaccine.



GRAPH 2.—Diagram showing the postvaccinal agglutinin changes for the paratyphoids in an individual following oral vaccine—mixed.

Results and Discussion. Of those cases (institution employee group) receiving oral vaccine, 19% had been vaccinated previously, 2% gave a history of typhoid and 11% were cases of arrested pulmonary tuberculosis. (The latter group shows a degree of non-specific reaction to the typhoid agglutination tests). In view of this, a total of 32% of the cases would likely manifest some degree of pre-vaccinal agglutinins. Three cases, with a history of recent food poisoning, had high titers for *Paratyphosus* β . Eleven per cent of the subcutaneous cases gave a history of previous vaccination or typhoid disease. Following the administration of the oral vaccine, there were no severe reactions. Thirteen per cent of the cases had a slight febrile reaction, none of which was above 38°C .; 33% had some symptomatic reaction, but in no case was the individual incapacitated (Table 1).

Following an interval of 60 hours, the titers of the "O" antigen fraction are the lowest of the series, the majority of cases ranging

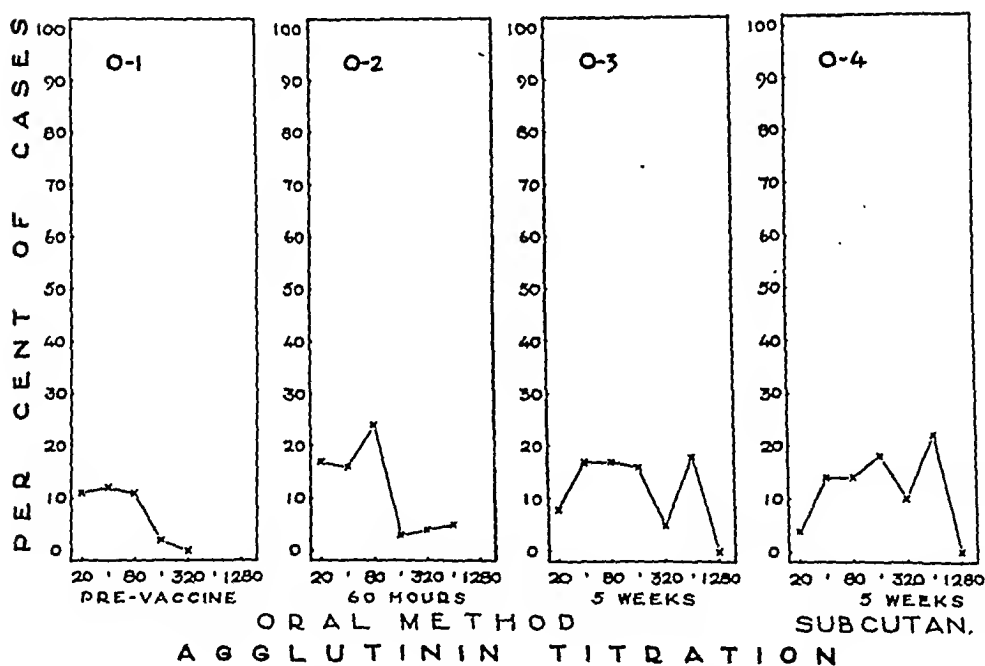
* Purchased from Eli Lilly Co., Indianapolis, Ind.

† Ten thousand million typhoid bacilli; 5000 million *Paratyphoid* α bacilli; 5000 million *Paratyphoid* β bacilli.

from 1 to 20 to 1 to 80. After an interval of 5 weeks the "O" titers continue to be the lowest of the series, but have increased both in number of cases and titration (Graph 3, O-3). The histograms of the oral and subcutaneous cases, at 5 weeks, are essentially comparable (Graph 3, O-3 and O-4).

TABLE 1.—SYMPTOMS FOLLOWING ORAL TYPHOID VACCINE—100 CASES.

Symptoms.	Cases.
Headache	14
Nausea	6
Malaise	4
Emesis—first capsule	3
Diarrhea—slight	2
Tenesmus	1
Orbital edema	1
Joint pains	1
Vertigo	1
Total	33

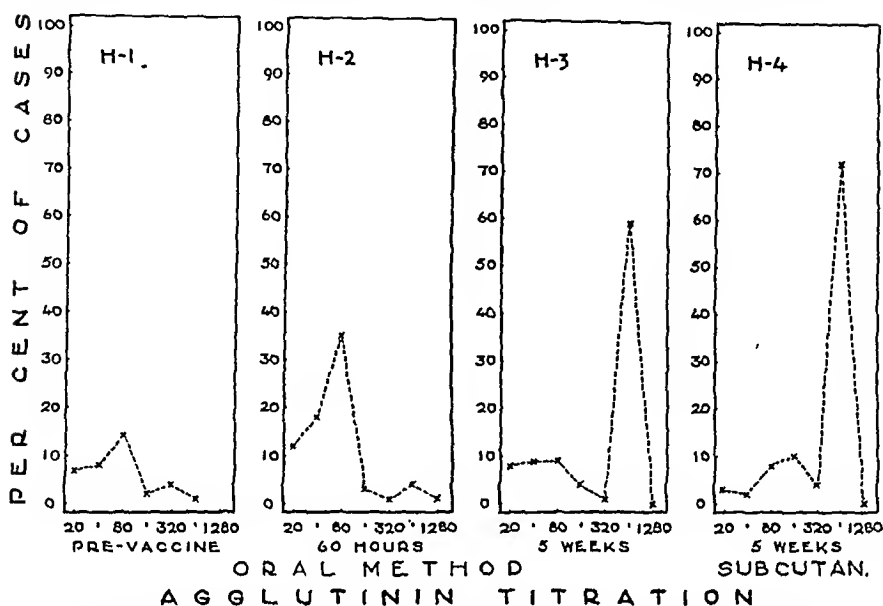


GRAPH 3.—Diagram showing distribution of cases according to agglutinin titration with the somatic antigen "O" of *E. typhosa* following administration of typhoid vaccine—mixed (oral method, 100 cases; subcutaneous method, 100 cases).

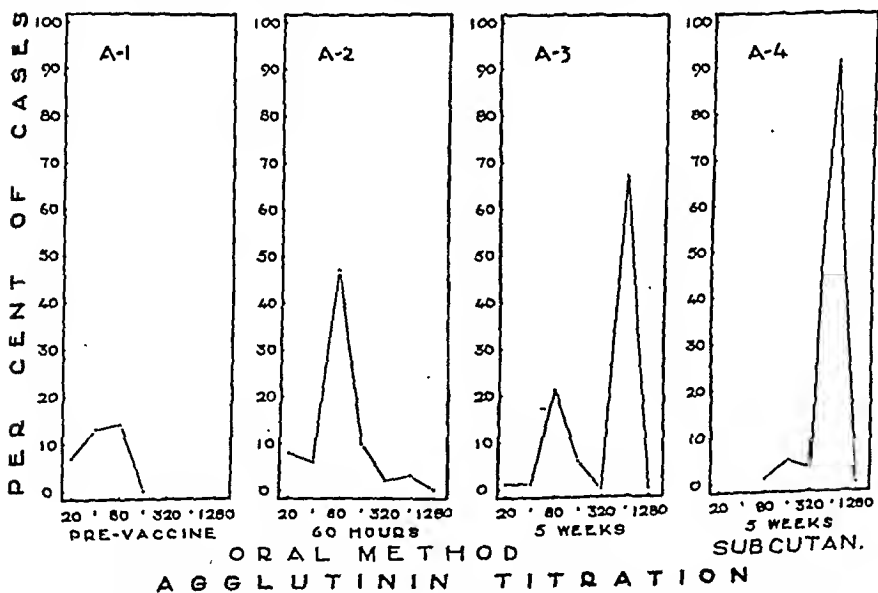
The maximum number of cases showed agglutinins with the "H" suspension in dilutions of 1 to 80 at 60 hours (Graph 4, H-2). The agglutinin titration increased to 1 to 640 at 5 weeks (Graph 4, H-3). This is contrary to the findings of Dennis and Berberian³ who found the "O" agglutinins were usually higher than the "H" agglutinins following oral vaccination.

In both the oral and subcutaneous methods, the "O" and "H" fractions of *E. typhosa* tend to be slower in the appearance of their agglutinins than do the paratyphoids.

The greatest number of cases responded to *Paratyphoid* α at 60 hours in dilutions of 1 to 80 (Graph 5, A-2) and to *Paratyphoid* β in

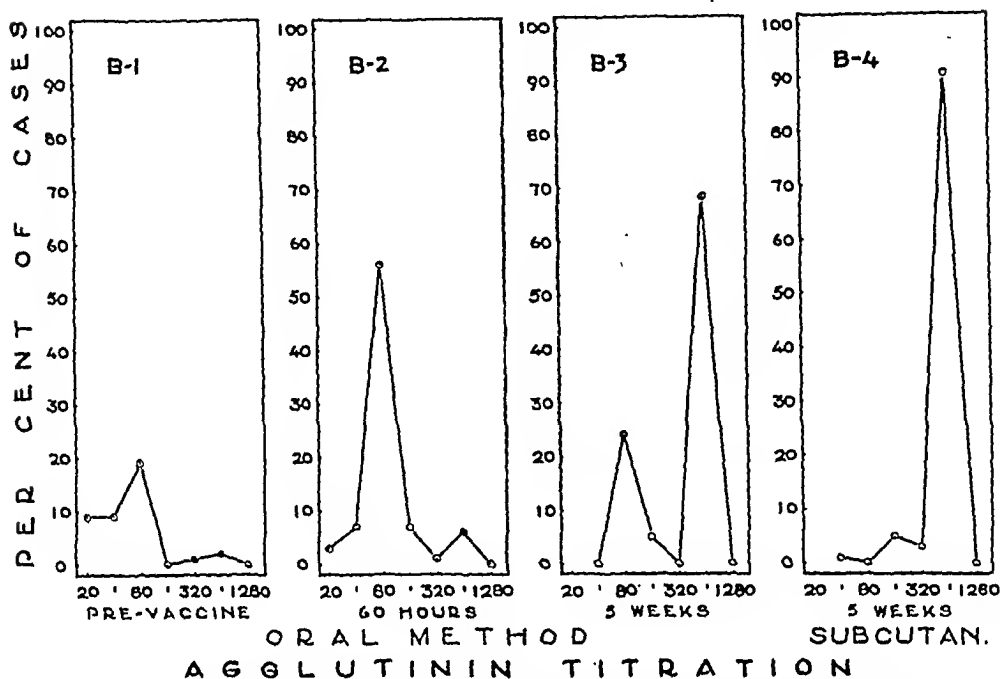


GRAPH 4.—Diagram showing distribution of cases according to agglutinin titration with the flagellar ("H") antigen of *E. typhosa* following administration of typhoid vaccine—mixed (oral method, 100 cases; subcutaneous method, 100 cases).

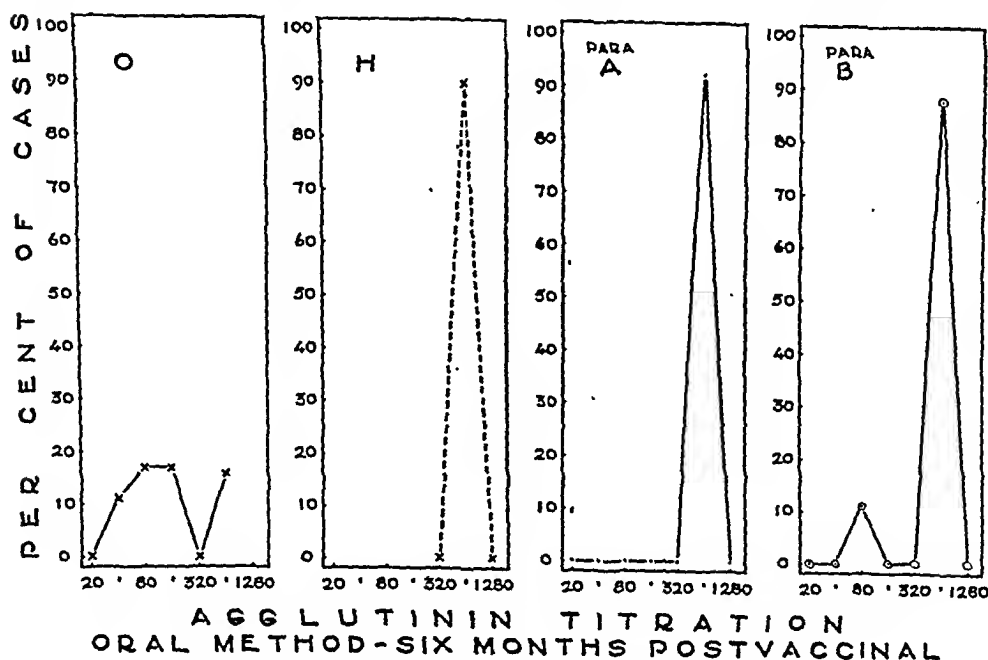


GRAPH 5.—Diagram showing distribution of cases according to agglutinin titration with the antigen of *S. paratyphi* (*Paratyphosus* α) following administration of typhoid vaccine—mixed (oral method, 100 cases; subcutaneous method, 100 cases).

dilutions of 1 to 80, but in greater numbers than with *Para* α (Graph 6, B-2). This demonstrates the well established fact that *Para*-



GRAPH 6.—Diagram showing distribution of cases according to agglutinin titration with the antigen of *S. schottmülleri* (*Paratyphus* β) following administration of typhoid vaccine—mixed (oral method, 100 cases; subcutaneous method, 100 cases).



GRAPH 7.—Diagram showing the persistence of typhoid agglutinins in the blood serum 6 months following oral vaccine.

typhoid α is less agglutinable than is *Paratyphoid* β . This is more apparent in the qualitative evaluation of the agglutinins. At 5 weeks both of the paratyphoids have the greatest number of cases with agglutinins in dilutions of 1 to 640, which is somewhat higher than is generally reported for the paratyphoids following vaccination. With the paratyphoids, about 20% more subcutaneous than oral cases developed agglutinins in the higher dilutions.

The agglutinin response following the oral method is shown almost simultaneously with the administration of the antigen. Generally speaking, significant titers are present at 60 hours following oral vaccine. The titers are higher following a single subcutaneous dose than following a single oral dose of vaccine. *The titers following the two methods are essentially comparable after 5 weeks.*

In the reëxamination of the oral cases, following a post-vaccinal period of 6 months, significant titers were present in the "O" fraction in 61% of the cases, in the "H" fraction in 90% and in each of the paratyphoids in 92 and 99%. There was a moderate recession of the "O" agglutinins, a progression of the "H" fraction, while the *Paratyphoid* α had increased in both numbers and titrations. *Paratyphoid* β showed slight gain in both cases and agglutinin titer (Graph 7).

In the present study, after a post-vaccinal period of 5 weeks, 24% of the subcutaneous and 8% of the oral cases failed to show agglutinins. This is in striking contrast to the recent report of Lacy and Cohen⁶ who reported the absence of agglutinins in 25% of the subcutaneous and 93.4% of the oral cases. The variance of results can best be accounted for by the difference in the antigen strains employed in the preparation of the respective vaccines. Lacy and Cohen⁶ used their own laboratory strain of organisms, which was formalinized in the preparation of their oral antigen.

In the preparation of a mixed typhoid vaccine, according to Topley,⁹ the organisms should possess the following characteristics: *B. typhosum*—smooth, motile, virulent strain, with flagellar antigen and surface antigen III; *B. paratyphoid*—smooth, motile, virulent strain, with flagellar antigen and surface antigen VI.

The Typhoral—mixed (Lilly) vaccine, according to the manufacturer, is prepared from the new U. S. Army Strain No. 58, as reported by Siler⁸ and "a virulent local strain, which caused a fatal case." Both are considered superior to the old Rawling strain. The organisms are heat killed and preserved with "Merthiolate." Moor and Brown⁷ used the same oral antigen as the present study with equally favorable results.

In view of the favorable clinical reports, the agglutinin response and the reduction of constitutional symptoms (as evidenced in the present study), the authors conclude that the oral method of typhoid vaccination merits favorable consideration and wider use.

Summary. 1. Using typhoid-mixed vaccine, 100 cases were vaccinated by the oral and a like number by the subcutaneous method. Blood serum agglutinins were determined periodically.

2. Thirty-three per cent of the cases which received the oral typhoid-mixed vaccine had mild reactions, none of which were incapacitating.

3. Significant agglutinin titers with oral typhoid vaccine are present within 60 hours. The agglutinin titration of both methods are essentially comparable after an interval of from 2 to 5 weeks. Significant titers persist for 6 months or longer following oral vaccine.

4. Those cases failing to show agglutinins 5 weeks following vaccination were 24% for the subcutaneous and 8% for the oral cases. Thus, the failures are three times as numerous with the subcutaneous as with the oral method.

5. The authors conclude, from the extensive clinical reports of others and the present laboratory results, that the oral method is as efficacious as the subcutaneous method of mixed typhoid vaccination.

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ACUTE INFECTIOUS GASTRO-ENTERITIS.

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With the apparent increase of acute digestive upsets associated with diarrhea, it would seem advisable to consider some of the problems presented by these cases. Certainly, we must agree that few conditions encountered by the physician in his daily rounds are as puzzling from the standpoint of an etiologic diagnosis as those associated with the acute onset of diarrhea. Diarrhea is only a symptom of disturbed intestinal function and may be produced by many conditions both within and without the bowel.

If our clinician be a careful systematic worker, he will, when confronted with a case of diarrhea, patiently go over the history, developing a clear story of the onset and progress of the symptoms, searching for any etiologic factors in dietary irregularities, group exposures, and so on. He will then make a complete physical exam-

ination, inspect the stools, and check the blood count. While doing these things, he will run over in his mind the various possibilities excluding many and restricting his preliminary diagnosis to a relatively small number. This number may be further decreased by stool cultures, agglutination tests, phage tests, and so on, but all too often after having done his utmost he will be forced to a diagnosis of diarrhea of unknown etiology.

If, on the other hand, our clinician is hurried or a bit casual or by past experience convinced that an etiologic diagnosis is unlikely, he will attempt to exclude the acute surgical conditions and then will readily accept the patient's statement that his symptoms are due to some food that he has eaten, or that he is suffering from intestinal "flu." However, the physician must frequently admit to himself the diagnosis of diarrhea of unknown etiology. Fortunately, these cases are usually relatively mild and of short duration so that insofar as the patient is concerned, he rarely suffers any ill effects from his incomplete diagnosis. On the other hand, from the physician's standpoint it is certainly a challenge to modern medicine that a condition approaching epidemic proportions is so frequently unexplained.

We have recently experienced in the San Francisco Bay area a fairly widespread outbreak of acute gastro-enteritis, both in institutional groups and the general population. These cases have been characterized by the acute and sudden onset of nausea, abdominal cramps, watery diarrhea, sometimes vomiting, slight headache, general aching, dizziness, and fever. In some cases there have been mild upper respiratory symptoms for a day or two before the explosive onset of the digestive symptoms. The most characteristic symptom was the explosive watery diarrhea, the number of stools varying from 2 to 20 or more per day. Tenesmus was rare and blood or mucus was very rarely seen in the stools. Temperature varied from normal to 104°. The average case was relatively mild and of short duration. However, complications may occur as evidenced by the development in 2 of our cases of acute appendicitis requiring operation.

During the last year, we have seen sporadic cases of this condition with greater frequency than in previous years but during the first part of December it approached epidemic proportions. Thus, at the Stanford University Hospital, 28 nurses and several members of the general hospital personnel were hospitalized for this type of disturbance between November 16th and January 15th, 20 of the admissions occurring between the 9th and 16th of December. During the same period a considerable but undetermined number of the hospital personnel were similarly affected but did not report for hospitalization. While this was occurring at Stanford Hospital, other institutional and industrial groups as well as the general population about the Bay area were experiencing the same difficulties.

The period of hospital confinement in this group of 28 nurses varied from 2 to 13 days with an average of 4.8 days. This does not include the hospital days for complications, nor have we figures for working days lost in this group after dismissal from the hospital nor for the days lost by those not hospitalized. However, these figures sufficiently emphasize the economic drain connected with such an outbreak.

Turning to a more detailed analysis of the symptoms in our cases, we find diarrhea present in all. The stools varied from 2 to 17 per day, were usually small, watery, light yellow, free from mucus and gross inflammatory elements, although showing an increase in pus cells microscopically. One of our cases showed macroscopic blood in the stools and I am informed that several cases reporting at the emergency hospital also showed blood in the stools.

Fever was present in 25, ranging from slight to 104° , usually dropping sharply to normal in 2 or 3 days. Abdominal cramps usually preceded the bowel movements and at times were quite severe. The bedside records mention the occurrence of nausea, vomiting, headache, backache, nasal congestion, sore throat, and chills.

Careful blood counts were made by Dr. Wyckoff's staff at Stanford University Hospital on 25 of these patients; 14 showed white blood counts under 10,000, 8 ran from 11,600 to 14,500, and 3 ran over 20,000. The polymorphonuclears varied from 37 to 93%, 9 being below 65% and 16 above 65%; 22 had a definite left nuclear shift with a banded count of 10% or higher; 62% was the highest relative count and 10,971 was the highest actual banded count. Eight cases had an eosinophilic count ranging from 1 to 7%, the highest actual eosinophilic count being 1248. Dr. Wyckoff calls attention to the fact that it is unusual with a left nuclear shift to have the eosinophilic elements persist and that this is not ordinarily seen with bacillary infections. From these counts, it is evident that our cases present no characteristic blood picture.

Stool cultures were carried out on 13 cases. In 10, there appeared a growth of Gram-negative bacilli giving the sugar reactions of the typhoid-dysentery group but as yet defying exact classification. In the serologic tests using *B. typhosus*, *B. Flexner W*, *B. Flexner Z*, *B. dysenteriae Y*, and *B. dysenteriae Sonne*, antisera, there was but one agglutination that might be taken as significant.

We were frankly surprised to find the high percentage of cultures showing the characteristics of the typhoid dysentery group but still did not feel convinced of their etiologic importance. Further cultural studies are being carried on, but when it is recalled that there are probably about 50 types of dysentery bacilli divided among 3 main groups 1, Shiga; 2, Flexner, and 3, Sonne—having different cultural characteristics, the difficulties of pursuing this study in a busy laboratory are evident. An additional difficulty

in evaluating the etiologic significance of these organisms is that some of these atypical strains will not agglutinate with the standard type sera, so that the diagnostic value of the agglutination test is greatly decreased. Negative agglutination tests may be obtained in proven cases of bacillary dysentery if the laboratory does not include in its test antigen a strain similar to the one causing the infection.

Probably the most valuable use of the agglutination test in determining the etiologic significance of a specific organism isolated from the stool is to attempt to agglutinate it against the patient's own serum after his recovery. This test was carried out on 10 of these cases with negative results in all. Such a result certainly makes it seem unlikely that these organisms were the cause of the infection and much more likely that they were merely accidental invaders.

From this brief review of these cases which were in all ways apparently similar to cases occurring in other institutions and the general population about the Bay area, it seems evident that we were dealing with an acute infectious gastro-enteritis of undetermined etiology.

Outbreaks of diarrhea are all too common in isolated institutions and can frequently be traced to food poisonings or to infection with one of the bacillary dysentery group. In connection with such outbreaks an important possible source of infection has recently been called to our attention by the sanitary engineers. Largely stimulated by the outbreak of amebiasis in the Chicago hotels, the whole subject of contamination of the water supply within buildings has been carefully studied and many surprising possibilities brought to light. Thus, any plumbing fixture in which the intake pipe takes off directly from the supply pipe and enters below the highest water level in the container may under certain conditions act as a syphon and draw the material in the container directly into the supply pipes. All that is necessary is that there shall be a temporary vacuum in the supply pipe such as is produced by shutting off the pressure in the mains, draining the supply pipe in a dwelling, or, in large buildings, by sudden excessive use on the lower floors. As a public health menace, the flush valve type of toilet is the most dangerous and it has been demonstrated that frequently this syphonage does occur.*

I recently spent some time with Dean Morris of the Engineering Department of the Stanford University and he had some interesting stories to tell. In one of the most modern homes on the campus equipped with the latest bathroom fixtures, it was demonstrated that coloring matter placed in the toilet bowl on the second floor

* Plumbing regulations now in force in most communities require the presence of a syphon breaker in all new flushometer valve installations. The danger of syphonage, of course, continues in older fixtures not equipped with the syphon breaker.—
EDITOR.

could be recovered from the water faucet in the kitchen by merely shutting off the street supply valve and drawing water on the lower floors. A somewhat similar but more dramatic demonstration was the plumber who was called to repair a toilet that refused to drain; having inspected it, he went to the basement, shut off the supply valve, and drained the pipes. Imagine his surprise but hardly gratification when, on returning to the disordered toilet, he found it emptied, the contents having been syphoned back into the water pipes. There are many more stories, illustrating the possibility of contaminating the water supply if a negative pressure occurs in the supply pipes. At Claremont Colleges, they are convinced that since the correction of their plumbing arrangements, they have been free from the recurring outbreaks of diarrhea present before.

In this connection, the following letter from Dr. J. R. Griggs, the college physician at Claremont Colleges, is of interest. He states that "prior to the change in our plumbing system we have had epidemics of gastro-enteritis in which several dozen students would be simultaneously disabled with vomiting, diarrhea, abdominal cramps, fever 100-103, headache and varying degrees of toxicity. Most of them were ill for twenty-four hours to several days and were quite weak on recovery. Such outbreaks occurred usually in October or November and were repeated once or twice during the year. Apparently they became progressively worse gradually over a period of many years. Between the epidemics there were practically always individual sporadic cases of the same disease.

"Repeated samples of water and milk for culture failed to reveal the cause of the trouble. A great variety of causes and sources were suspected. A few cases occurring among townspeople led to the belief that the whole city water supply was contaminated by alvine discharges from the mountain cottages up the canyon. The method of fertilization and spray of the fresh vegetables and fruits was incriminated. Food handlers were scrutinized. Even the Santa Ana winds from the desert were suspected as the cause. The County Health Department repeatedly investigated and gave the colleges a clean bill of health.

"After much collaboration with pathologists, epidemiologists, and sanitary engineers it was found that eosin placed in toilet bowls could be recovered in the tap water because of back siphonage. Accordingly, vacuum breakers were installed on all toilets of the flushometer type in all college buildings, last year.

"Since September when I came here, we have had no epidemics of the old disease. In fact, no more than 3 persons have been ill at any one time with gastro-enteritis of any nature. Only 2 cases have approached the severity of the old 'plague.' There have, however, been nearly two dozen single sporadic cases of diarrhea, some with nausea, scattered throughout the past semester and throughout the student body of 1000 students. Two cases occurring

together were traced to an outside eating house, Mexican. Several others came back from holidays into Mexico. Two others were traced to homecured raisins. The rest have apparently originated here but have not had any epidemic characteristics."

Confirming these reports, W. Scott Johnson recently made a survey of 6 milk plants in St. Louis and found "210 definite plumbing defects which were capable under favorable conditions of establishing cross connections between contaminated material and the plant water supply." He further states that "it is recognized that a partial vacuum may exist without warning in any water pipe system due to a number of causes such as a heavy drain in a main due to a fire or cutting off the water supply and draining lines for repairs. Such a vacuum has been shown to be capable of siphoning the contents of a flush valve type of toilet bowl in good working order into the water supply line." It is thus evident that there is a very definite public health problem connected with our modern plumbing and that constant vigilance is necessary.

In this particular outbreak, it seemed too widespread to be satisfactorily explained on the basis of a bacillary dysentery or a food poisoning. Turning to the literature for a possible explanation, we find that R. R. Spencer¹ under the title of "Unusually Mild Recurring Epidemic Simulating Food Infection" reported apparently similar cases. In 1933, H. A. Wildman² under the title of "Polytropic Enteronitis" (acute infectious gastro-enteritis, or Spencer's Disease), reported a study of 750 apparently similar cases occurring in college students between September, 1927, and June, 1932. From his study he concludes that this condition may occur at any time of the year, either in epidemic or sporadic form, that it is widely distributed, uninfluenced by climate, that no predisposing factors have been determined and the responsible organism is unknown, and that it is apparently spread by secretions from the nose and throat.

Atypical colon bacilli, atypical Flexner bacilli, and atypical organisms belonging to the genus *Salmonella* have been found in the stools though their presence may be purely coincidental.

He calls attention to the fact that epidemics of diarrhea have been frequent since the World War, and have occurred in close association with epidemics of influenza. Influenza does not confer immunity to this disease or *vice versa*. Immunity after this disease did not last more than 6 weeks in some cases. Cases developed within 24 to 48 hours after contact with a known case, and epidemics reached their peaks in from 3 to 5 days instead of from $\frac{1}{2}$ to 12 hours as occurs in food poisoning.

About 10% of his patients complained of respiratory tract symptoms. He noted the frequency of peripheral neuritis. Blood counts showed polymorphonuclear leukocytosis, sometimes followed by a secondary leukopenia. Acute symptoms usually lasted from 18 to

24 hours and were followed by rapid recovery although the diarrhea has lasted 2 or 3 weeks and marked dizziness in standing has lasted as long as 6 weeks in some cases.

He has divided his cases into six groups in the order of their frequency: Type I: Gastro-enteric: nausea, vomiting, diarrhea. Type II: Enterocolic: diarrhea, sometimes cramps. Type III: Gastric: anorexia, nausea, vomiting. Type IV: Neurocirculatory: dizziness, dull headache. Type V: Typhlo-appendiceal: like acute appendicitis except for diarrhea; dizziness on standing, dull headache, fever less constant, less marked and less sharply localized tenderness in lower right quadrant, and less rigidity of abdominal wall. Type VI: Colic: cramps or severe midabdominal pain, usually with constipation.

At Wooster College, Imlay, Michigan, the author reports from 3 to 5 distinct epidemics each year with a large number of sporadic cases through the year. There were no fatalities and no sequelæ. Occasionally, a case of acute appendicitis occurred as a complication.

Treatment at present is naturally purely symptomatic. Wildman, from his experience recommends: 1. Prompt and thorough evacuation of the intestinal tract with castor oil, 1 ounce; soda bicarbonate 1 ounce; and orange juice. 2. Abstinence from food for 24 hours. 3. Cleansing enema, 2 ounces of salt to a quart of water. 4. Atropine, 1/100 grain to 1/50 grain for nausea or vomiting. 5. Soft, bland diet later. 6. Sodium ricinoleate, from 18 to 120 grains in divided doses, after the castor oil. 7. Bismuth subnitrate. 8. Camphorated tincture of opium. 9. For dizziness: (a) abdominal binder; (b) ephedrine, $\frac{3}{8}$ grain. 10. Phenobarbital, and so forth, for nervousness. 11. Aspirin. 12. Salt solution subcutaneously. 13. Glucose solution intravenously.

From this review, it is evident that there is a fairly widespread gastro-enteritis occurring sporadically and at times in epidemics, of uncertain etiology, running a fairly typical course of short duration, and usually terminating in complete recovery. None of the atypical organisms so far reported in the stools can be accepted as of proven etiologic significance although there is room for further study. There is much to suggest that the primary infection in these cases is due to a filterable virus transmitted in the secretions from the nose and throat. The various organisms cultured from the stools are possibly only secondary invaders, such as the influenza bacillus has proven to be in influenza, and the various bacteria found in the nose and throat are in the common colds.

If we are dealing with a specific infectious gastro-enteritis due to a filterable virus, it is to be hoped that this will not show an increasing epidemic occurrence and the development of serious complications such as accompanied the pandemic of influenza.

My object in presenting this report is merely to emphasize the uncertainties that exist and to urge further discussion and research.

It is not a problem to be solved by the individual clinician, but his help is necessary in making promptly available to the public health and research laboratories material for study. From such a study it is reasonable to hope that information will eventually be forthcoming which will aid us as clinicians in more intelligent prevention, diagnosis, and treatment of acute gastro-enteritis.

Summary. 1. Acute gastro-enteritis seems to be occurring more frequently, both sporadically and in epidemics.

2. Many of these cases are diagnosed as diarrhea of unknown etiology.

3. Our modern plumbing offers many opportunities for contamination of the water supply within industrial plants, office buildings, and private dwellings.

4. It is suggested that there is an acute infectious gastro-enteritis probably due to a filterable virus, carried by the secretion of the upper respiratory tract.

5. It is urged that all outbreaks of diarrhea be reported immediately to the proper authorities for careful investigation.

6. With the accumulation and spread of more exact knowledge many outbreaks may be prevented.

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THE ETIOLOGY OF EFFORT SYNDROME.*

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Effort syndrome is a condition characterized by breathlessness, sighing, "dizziness or faintness," fatigue, palpitation, tachycardia, precordial pain and tremor, and is precipitated by exertion or anxiety. It is probably the commonest source of error in the differential diagnosis of organic cardiac disease. While it has been well recognized that effort syndrome is frequently associated with anxiety states, its etiology has remained obscure. Sir Thomas Lewis⁴³ suggested that a diminution in the buffer substances in the blood was a possible cause. More recently, especial attention has been given to the symptoms of sighing and of the related respiratory disturbances. White and Hahn⁷¹ found that

* Supported in part by the Christine Breon Fund for Medical Research.

80% of 100 patients suffering from effort syndrome sighed excessively, whereas only 19% of 400 normal controls showed the same phenomenon. These writers stated that the total ventilation in at least one of their patients was normal, although from recent work on respiration by Shock and Soley⁶⁶ it becomes evident that she was hyperventilating. Baker⁴ studied a group of patients with the symptoms of sighing, breathlessness, fatigue, palpitation and inframammary pain and concluded that the etiology was obscure and "treatment by no means always successful." Maytum and Willius⁴⁸ were the first to recognize the relation of hyperventilation to the symptoms described by these and many other authors.

Under the leadership of Dr. W. J. Kerr, a series of studies on the anxiety states and the hyperventilation syndrome has been carried out at the University of California Hospital.

Our purpose in this paper is to point out the relation of the symptoms of patients suffering from effort syndrome to the respiratory disturbances and to the shift in the acid-base equilibrium resulting from excessive loss of carbon dioxide from the lungs. Some or all of the symptoms of which these patients complained were reproduced by deep breathing at the rate of 25 to 30 respirations per minute. However, even when this respiratory rate was maintained, the symptoms were relieved when 2% CO₂ was added to room air, and the sensation of suffocation disappeared and breathing became subjectively easier.

In view of these findings, it was felt that a study of the acid-base equilibrium of the blood of these patients might show (1) whether a relative respiratory alkalosis was present chronically, and (2) whether the symptoms were related to the acid-base balance. Hence, acid-base determinations of the blood of 7 patients were made under basal conditions and during a period of voluntary hyperventilation in which their symptoms were precipitated. We are reporting in detail the history and experimental results in 1 of these patients, and are including charts (Fig. 3) demonstrating the changes in the pH, pCO₂ (CO₂ tension) and blood bicarbonate in 6 other cases.

Case History. E. C. B., a 27-year-old white, divorced housewife, first came to the University of California Clinic on June 2, 1932, complaining of palpitation. For several years she had been afflicted with palpitation, shortness of breath, dyspnea on exertion, precordial pain and fatigue.

There were no familial diseases. Both parents were living and were supported by the patient.

She had had the usual childhood diseases. Tonsillectomy and adenoidectomy had been performed at the age of 10, and appendectomy at the age of 22. In 1931, she had had a spinal injury. She had been married in 1925 and divorced shortly afterwards. She had 1 child living and well. There had been no other pregnancies.

On examination, the patient was found to be a well-developed and well-nourished woman. Many teeth were carious. The thyroid was thought to be slightly enlarged. A soft systolic murmur was heard at the apex.

The blood pressure was 120 mm. Hg. systolic and 86 diastolic. The examiner stated that there was possible left-sided cardiac enlargement and questionable edema of the ankles.

Laboratory. The first specimen of urine was acid, contained no albumin, showed green reduction, and contained 8 to 10 white blood cells in the sediment per high-power field; a later specimen was acid, had a specific gravity of 1.030, and contained no albumin or sugar and only an occasional white blood cell per high-power field. The Wassermann reaction of the blood was negative. Fluoroscopy showed the heart to be normal in size. An electrocardiogram showed a rate of 100, *P-R* interval of 0.19 second and inverted T_s .

Course. The patient was admitted to the hospital in August, 1932, for further study. Laboratory procedures on entry gave the following findings: Blood: 78% hemoglobin, 4,750,000 red blood cells, 7,680 white blood cells; the smear and differential count were normal. The stool was normal. Basal metabolic rate was 3%+. Dental roentgenograms showed several fractured root fragments, pyorrhea and one apical abscess. Diagnoses were made of (1) neurocirculatory asthenia and (2) dental caries.

After her discharge from the hospital the patient was followed in the clinic. In November, 1932, she strained her back. Later she received treatment for a retroverted uterus and menorrhagia. In March, 1935, there was a normal P.S.P. excretion by the kidneys. In May, 1935, a Webster suspension of the uterus was done because of low abdominal pain.

In December, 1936, she was able to give a much more accurate story of the symptoms which had bothered her persistently since she was first seen by us. She stated that these symptoms came in attacks which began with difficult, deep breathing followed by rapid heart rate, dizziness, constriction of her throat, suffocation, numbness of her hands and feet, extreme fatigue and finally diuresis. All of these symptoms were reproduced by a short period of hyperventilation (about $2\frac{1}{2}$ minutes) and were relieved when she continued to hyperventilate while breathing CO_2 . At this time physical examination was essentially negative. The thyroid was palpable but was normal in size. Fluoroscopy showed a heart of normal size with slight prominence of the pulmonary conus. On December 21, 1936, her basal metabolic rate was 9%+. A gastric analysis was normal. An electrocardiogram was normal. Fear of discovery of her illicit relations with several male acquaintances, as well as exertion, definitely initiated her attacks.

The final diagnosis was "anxiety state complicated by the hyperventilation syndrome." She was treated by explanation and demonstration of the cause of her symptoms, by administration of bromides and ammonium chloride, and by instruction in abdominal breathing and in the use of a paper bag for rebreathing during attacks. She improved rapidly and had only mild attacks occurring rarely until she was last seen on August 17, 1937.

Experimental Method. The subject, E. C. B., was brought to the laboratory in a fasting condition. After a rest of 45 minutes, the basal metabolism was determined in triplicate by the Tissot open-circuit method using a Siebe-Gorman half-mask. Six determinations each of pulse rate and blood pressure were made during this period. After the last metabolism sample of 10 minutes, the mask was removed and a control blood sample drawn from the finger tip for estimation of the acid-base balance of the blood by the Shock and Hastings micro-methods.⁶⁵ After the patient had rested 5 minutes, the mask was readjusted and voluntary overbreathing at the rate of 28 to 32 respirations per minute was begun and maintained for 10 minutes. The expired air was collected continuously in 2-minute samples for measurement of the respiratory volume and analysis of CO_2 and O_2 content by the Haldane technique. One-half-cc.-samples of blood

were drawn from the finger tips at 2-minute intervals during the period of hyperventilation. After the cessation of overbreathing, the collection of expired air was continued for 15 minutes in order to observe the recovery curve.

TABLE 1.—CHANGES IN RESPIRATION AND BLOOD CHEMISTRY WITH SPONTANEOUS HYPERVENTILATION AND WITH HYPERVENTILATION CAUSED BY BREATHING 11% CARBON DIOXIDE.

(Subject: E. C. B., January 9, 1937.)

Time (min.).		Expired air, l per min.	Metabolism, % of basal.	O ₂ uptake, cc. per kg. per min.	% CO ₂ in expired air.	% O ₂ in expired air.	CO ₂ expired, cc. per min.	% red blood cells in blood.	pHs at 38° C.	(CO ₂) _b , mM. per l.	pCO ₂ , mm. of Hg.	(BHCO ₃) _s , mM. per l.
End of interval.	Middle of interval.											
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)
Basal	0	4.18	100	3.22	3.61	16.67	149	0.41	7.39	21.36	41.1	24.2
1.55	0.78	18.46	205	6.66	2.90	18.69	535					
	1.00	0.41	7.45	20.46	34.9	23.5
2.58	2.07											
3.60	3.09	19.23	195	6.31	2.40	18.94	461					
5.73	4.67	17.69	171	5.54	2.15	19.06	380					
	5.00	0.41	7.53	19.33	28.0	22.7
7.78	6.75	15.55	167	5.42	2.13	18.90	331					
	7.60	0.41	7.55	19.77	27.4	23.1
9.97	8.87	14.14	165	5.35	2.18	18.76	308					
	9.50	Hyper	ventilation	0.41	7.50	18.93	29.1	22.1
10.00	Stop											
12.50	11.23	3.92	101	3.26	2.37	16.67	93					
	12.00	0.41	7.47	19.14	31.5	22.2
17.56	15.03	3.08	102	3.33	2.66	15.46	82					
	17.00	0.41	7.42	20.93	38.0	23.9
26.02	21.79	4.19	115	3.75	2.88	16.27	121					
	25.00	0.42	7.38	22.13	43.7	24.9
27.52	26.76						No sample					
	27.00	Start	Breathing	11% CO ₂								
28.63	28.08	27.90	10.1							
29.38	29.01	45.36	10.5			0.42	7.18	25.30	65.8	23.7
	29.38	Stop	Breathing	11% CO ₂								
31.01	30.20	21.08	149	4.84	4.28	18.99	902					
38.80	34.90	4.84	108	3.48	3.85	16.86	186					
45.21	42.02	4.80	107	3.47	3.66	16.88	176					

Basal Data.

BMR*	-0.39	-1.4	-4.1
Pulse rate	...	88	74	82	81	79
B.P.	...	114/84	114/81	113/83	101/81	110/80
Resp. rate	...	17	17	18		112/79
Height	...	150.5 cm.				
Weight	...	57.4 kg.				
Age	...	27 years				

* Boothby-Sandiford norms.

Results. From Table 1 and Figure 1 it is evident that the respiratory volume increased from 4.1 to 19.23 liters per minute during the first 4 minutes of the period of overbreathing but decreased

somewhat during the last 6 minutes. The rise in the pH of the blood from 7.39 to 7.55, the fall in pCO_2 from 41 to 27 mm., and the slight but progressive decrease in the bicarbonate of the serum from 24.2 mM per liter (53.2 volumes %) to 22.1 mM per liter

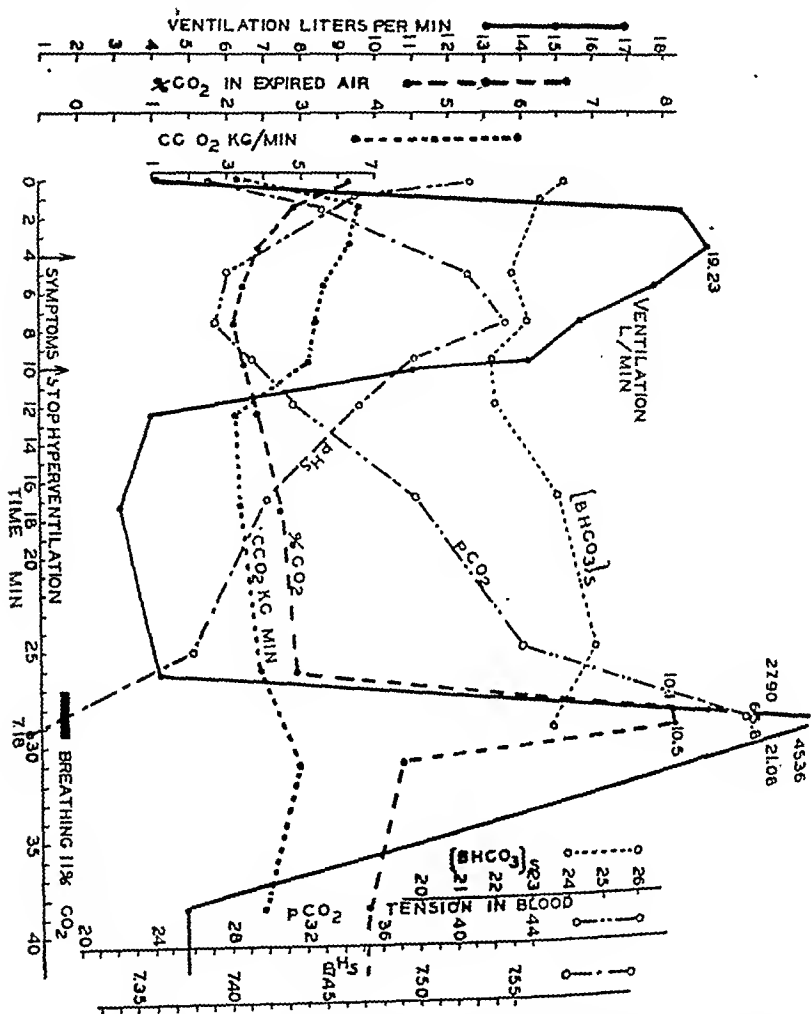


FIG. 1.—Changes in respiration and blood chemistry with hyperventilation and breathing 11% CO_2 . — ventilation volume in liters per minute. --- bicarbonate content of blood serum. — pH of blood serum. — CO_2 tension of arterial blood. — % CO_2 in expired air. O_2 consumption measured as cc. of O_2 per kg. per minute.

(48.6 vol. %) are shown in Table 1. The symptoms of dizziness, fatigue, palpitation, constriction in the chest and throat and sense of "suffocation," headache, numbness of the hands and feet and finally frank tetany, began at the fourth minute and were fully established at the end of the fifth minute. The oxygen consump-

tion increased by 100% during the early part of the experiment. The CO_2 content of the expired air fell constantly (as is shown in the curve in Fig. 1) from 3.6 to 2.2%, but it should be noted that the total output of CO_2 increased from 149 to 308 cc. per minute. Hyperventilation was stopped at the tenth minute but the compensatory apnea which is marked in normal subjects⁶⁵ at the cessation of overbreathing was slight in this patient. The return of the pH of the blood was slower than in normal subjects, although practically complete in 15 minutes. Some of the symptoms were still present after 25 minutes, probably because of the slower restoration to normal of acid-base balance in the tissue fluids than in the blood. Twenty-seven minutes after the experiment started, a mixture of air with 11% CO_2 was administered, which increased the ventilation volume to 45.36 liters per minute, but at the same time relieved the headache, palpitation, precordial pain, paresthesias and muscle cramps. This high concentration of CO_2 was so uncomfortable for the patient that it was continued for only $2\frac{1}{2}$ minutes. After the patient had breathed CO_2 for 2 minutes, a blood sample was found to have a pH of 7.18 and a bicarbonate content of 23.7 mM per liter (52.14 volumes %).

The alterations in acid-base equilibrium are more readily visualized in Figure 2, in which the data have been plotted on tri-axial coördinates (Hastings and Shock⁶⁵). In this chart pH lines run vertically, bicarbonate lines run from upper left to lower right, and CO_2 tension lines from upper right to lower left. All three scales intersect at 120 degrees and the bicarbonate and pCO_2 scales are logistic. This system provides maximal dissociation between respiratory and metabolic factors in acid-base equilibrium since it has been shown that CO_2 titration curves lie along the line "xy," and fixed acid changes take place along the line "AB" which is perpendicular to the respiratory line "xy." In Figure 2, the experimental points are numbered consecutively, and the path of displacement during 10 minutes of hyperventilation and the path during recovery are shown. Peters, Bulger, Eisenman and Lee,⁵⁶ Myers and Booher⁵³ and Hartmann and Smyth³³ have stated that tetany appears at a pH of 7.6 in normal individuals, but Hastings and Shock⁶⁵ noted symptoms of tetany in subjects when the pH was displaced to 7.55 by 15 to 20 minutes of hyperventilation. The patient, E. C. B., developed signs and symptoms of tetany after 5 minutes of hyperventilation when the pH reached 7.5, although at the onset of overbreathing the pH was normal. Furthermore, comparison with data on normal subjects⁶⁵ indicates that the patient's recovery was normal in direction but slow. From these data it is evident that she had symptoms of tetany before the pH had shifted as far toward the alkaline side as is necessary for the development of tetany in normal individuals, and that her recovery was slower than that of normal persons.

The displacement of the acid-base equilibrium by the breathing of 11% CO_2 for 2 minutes is shown in Figure 2 at point "A." The divergence of the path from the theoretical line "xy" is in all probability due to the short period of administration of CO_2 , which caused a rapid rise in the pCO_2 without attainment of equilibrium

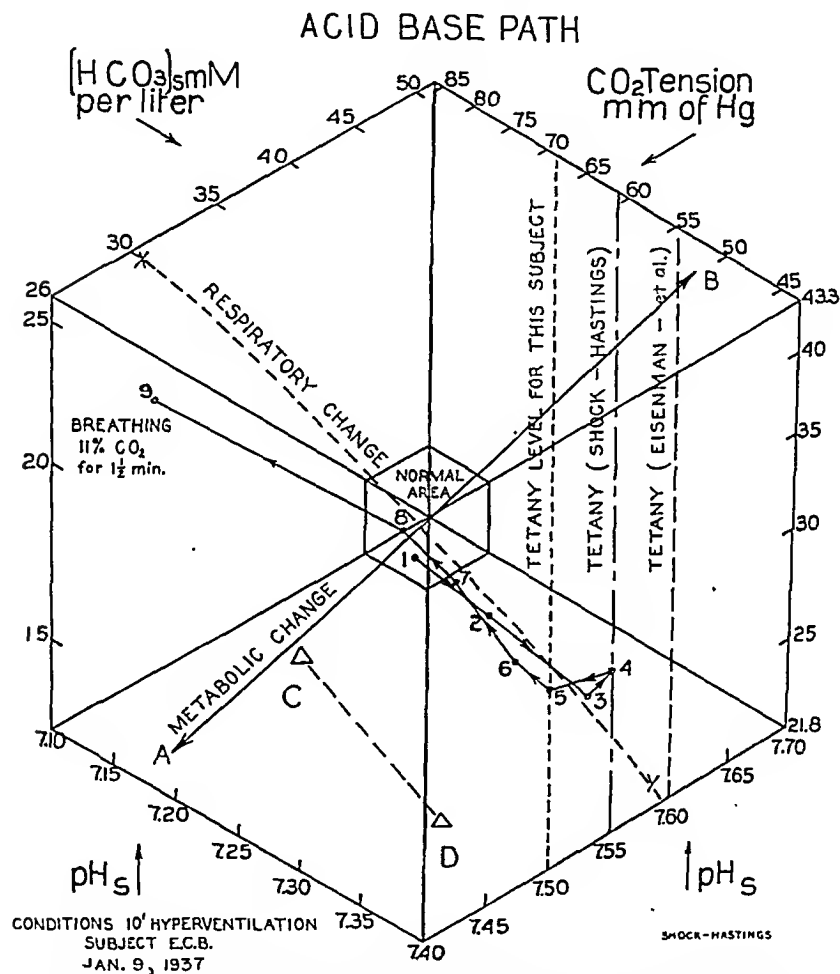


FIG. 2.—Change in acid-base balance of the blood produced by hyperventilation for 10 minutes in patient E. C. B. See text for explanation of coördinates.

of the bicarbonate content. Unfortunately, the CO_2 and air mixture had not been analyzed until after it was administered. A satisfactory mixture contains between 2 and 5% CO_2 .

Discussion. The symptoms of effort syndrome can be explained clearly when its relation to the hyperventilation syndrome is recognized. The symptomatology and the biochemical and physiologic

changes 1, 3, 6, 8, 9, 11, 14, 16-20, 22, 23, 25-29, 34-37, 39-41, 44-47, 49, 51, 52, 54, 57, 58-60, 63, 64a, b, 67-70, 72a, b which occur during hyperventilation have been reported adequately. It has been shown that the shift in the acid-base bal-

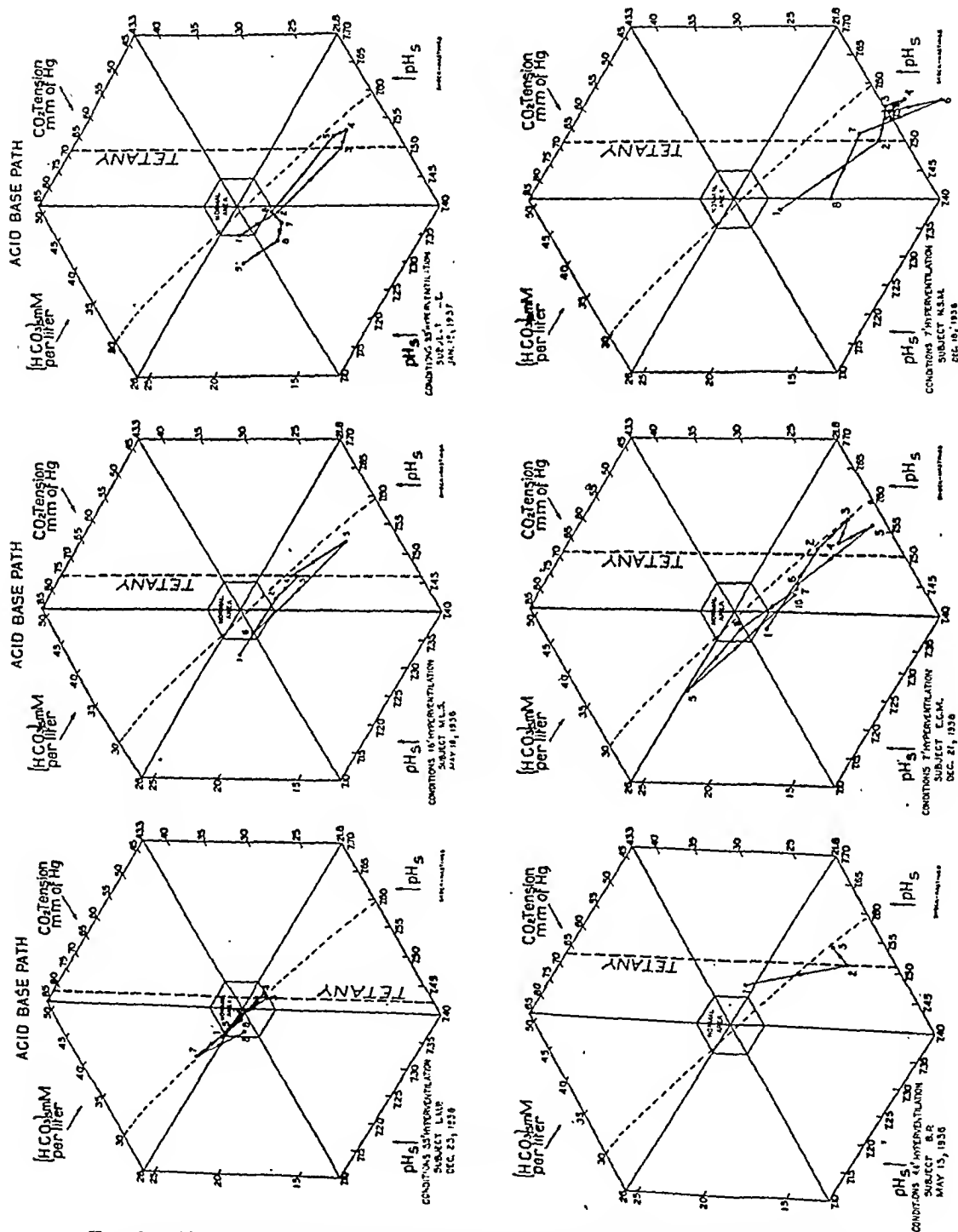


FIG. 3.—Alterations in acid-base balance of blood produced by hyperventilation in patients suffering from "effort syndrome." For explanation of coordinates see text.

ance toward the alkaline side, rather than any change in the calcium and phosphorus metabolism^{16 26 28 55 65} is responsible for the symptoms. While hyperventilation may be caused by anoxemia,^{21 24 31 62} organic nervous diseases,^{5 32} hot baths and hyperthermia,^{2 7 10 12 30 38 42} and anxiety and effort,^{13 41 47 72b} we are most interested in the two causes last mentioned, since it has been recognized that the combination of anxiety and effort produces the symptoms listed variously under the diagnoses of "soldier's heart," disordered action of the heart (D.A.H.), "neurocirculatory asthenia" and "effort syndrome." Most of these symptoms require no further explanation but there are several points which need clarification.

The sense of suffocation is probably due to cerebral anoxemia. Increase in total oxygen consumption during overbreathing is not incompatible with cerebral anoxemia, since the latter is a local condition due to vasoconstriction. Cobb and Fremont-Smith¹⁵ and Wolff and Lennox⁷³ have demonstrated that hyperpnea causes cerebral vasoconstriction. Mond and Wassermann⁵⁰ have stated that sighing respiration is one of the signs of cardiac dyspnea, presumably on the basis of cerebral anoxemia. Administration of carbon dioxide has been shown to relieve Cheyne-Stokes respiration, sighing and the sense of suffocation, probably by relieving cerebral vasoconstriction and consequently cerebral anoxemia.

Many of the patients with effort syndrome show periodic or suspirous breathing on the spiograms obtained during the determination of the basal metabolic rate by the Benedict-Roth apparatus and many patients are actually hyperventilating during the test. In our experimental work, the metabolic rate rose to levels of 100 to 180% above the basal level when the patients hyperventilated. Part of the increase in metabolism may be due to the muscular work of overbreathing, to alkalosis, to increased secretion of epinephrine or to combinations of these factors. But part of the effect is more apparent than real. When hyperventilation is begun, there is a washing out of alveolar air so that the CO₂ content of the expired air will be higher and the O₂ content will be lower than is normal. This lowered O₂ content will appear as an increase in O₂ consumption which is maximal during the early stages of hyperventilation. Conversely, when hyperventilation ceases, the O₂ content of alveolar air is appreciably higher than normal. Restoration of the normal alveolar O₂ concentration is brought about by the absorption of O₂ into the body from the alveolar air. Until the extra oxygen present in the alveoli is absorbed and a normal alveolar O₂ concentration is restored, analyses of the expired air will show a decrease in the amount of oxygen used. If we assume that the residual air represents alveolar air with an average value of 1 liter in normal subjects, then altering the oxygen concentration from 19.5 to 15% would make 45 cc. of oxygen available. If the basal oxygen consumption were 200 cc. per minute, the oxygen uptake

observed during the first minute following hyperventilation would be reduced by approximately 25%. Herxheimer and Kost³⁷ postulated that the decreased oxygen consumption following hyperventilation represents oxygen storage by some unknown mechanism within the body or by actual increase in oxidative efficiency resulting from preceding excessive ventilation. We believe, however, that the change in alveolar oxygen tension accounts for the apparent decrease in oxygen consumption.

We have been impressed by the peripheral vasoconstriction which is so marked during forced overbreathing that the fingers must be stabbed deeply to obtain blood for chemical studies. This has been noted previously by Schneider and Truesdell.⁶² The vasoconstriction results in a lowered oxygen saturation which tends to minimize the extent of the measured respiratory alkalosis.⁶⁵ Undoubtedly, blood obtained by arterial puncture would show an even greater pH displacement than we have demonstrated in finger blood, because the latter must contain some tissue fluid not yet in equilibrium with the circulating blood.

It must be made clear that the shift in acid-base equilibrium produced by hyperventilation is along the respiratory axis, line "xy" in Figure 2. This type of displacement involves changes in $p\text{CO}_2$ and pH primarily. Inspiration of CO_2 will alleviate the symptoms by replacing the CO_2 lost by overbreathing and the $p\text{CO}_2$ and pH values will return to normal along the same "respiratory axis" in the reverse direction. Previous experiments⁶⁵ have shown that changes of this kind take place very rapidly. The pH can be shifted toward the alkaline side also by displacing the acid-base equilibrium along the "metabolic axis" graphed as line "AB" in Figure 2. The administration of acids or such acidifying salts as NH_4Cl and CaCl_2 will prevent the symptoms in patients who hyperventilate because the pH is on the acid side (point "C" in Fig. 2) before they begin to overbreathe. Consequently, even though the pH is displaced to the same extent (to point "D" in Fig. 2), the level at which tetany appears is not reached. Thus the apparent anomaly of producing a metabolic shift as therapy for a respiratory shift is explained.

Fortified with a knowledge of the etiology of effort syndrome, we are now in a position to treat this condition rationally. An impressive method of approach to the patient is to have him hyperventilate to the point of production of symptoms and then have him continue to overbreathe air to which 2 to 5% CO_2 has been added (a tank of the gas mixture connected to the usual anesthetic bag and mask may be used). The CO_2 mixture relieves the symptoms within 15 to 30 seconds. When the patient realizes that the doctor understands the cause of his trouble, the first hurdle in treatment is passed.

The next step is to prescribe measures which will prevent over-

breathing or counteract the resulting alkalosis when overbreathing has occurred. The patient may be taught to breathe abdominally so that, even though the respiratory rate increases, the total ventilation is far less than it would be either with chest breathing or with chest and abdominal breathing combined. Sedatives may be prescribed to raise the patient's threshold of sensitivity to all stimuli. Ammonium chloride in doses up to 45 grains a day will tend to produce an acidosis, so that even though the patient hyperventilates to the same degree as previously, the pH will not be shifted to the point of tetany. Since so many of these patients have gastric anacidity, hydrochloric acid may be added to help in the production of acidosis. It should be stressed that, in sufferers from anxiety states complicated by the hyperventilation syndrome, treatment with sedatives, acidifying drugs and diets is merely a temporary measure to carry the patients along comfortably while psychiatric investigation of the anxiety is undertaken. The general practitioner or internist may be able to discover and relieve the anxiety although in many cases study by a competent psychiatrist is required.

The old terminology of effort syndrome should be discarded and a more descriptive term employed expressive of its etiology. Thus the diagnosis might be "anxiety state with (or complicated by) the hyperventilation syndrome." Such a diagnosis is commonly used to describe this condition in the records of the University of California Hospital.

Conclusion. The respiratory alkalosis resulting from hyperventilation produces the symptoms of effort syndrome.

Grateful acknowledgment is made to Kathryn Heck, A.B.M.A., and to the WPA (A.P.N. 165-03-6070) for clerical and statistical assistance in the analysis of the data.

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CIGARETTE SMOKING.

I. AS A CAUSE OF FATIGUE; II. EFFECT ON THE ELECTROCARDIOGRAM WITH AND WITHOUT THE USE OF FILTERS.

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It is a generally established fact that tobacco smoking may have deleterious results that seem to be overshadowed by the greater momentary pleasurable effects. Its use definitely becomes a habit^{8,13} which is discontinued only with more or less difficulty. As a result, many of us have accepted it as a matter of fact and frequently do

not carefully consider the effect of smoking on the symptomatology of our patients.

This study began as a result of the *unsuccessful treatment* of 2 patients who complained of fatigue. Both suffered mainly from this symptom for a number of years. All sorts of medication had been of no avail. One of these patients noted that his pulse rate increased considerably every time he smoked a cigarette. As a result of this the question of tobacco as the cause of the fatigue arose. Both patients improved and gained weight after cessation of smoking.

TABLE 1.—CASES OF FATIGUE RELIEVED BY CESSATION OF CIGARETTE SMOKING.

Case.	Sex.	Age.	History.	No. of cigarettes daily.	Effect of cigarette smoking on the heart rate.		Condition after cessation of smoking.
					Before smoking.	After smoking.	
W. C.	M	37	Extremely tired past 3 years. Pains left chest. No relief from sedatives or thyroid extract.	20	80	100	Patient gained 10 pounds; felt greatly improved. Was not tired.
E. S.	F	23	Tired past year. Loss of weight.	10-15	80	125	Gained 4 pounds in 3 weeks. Not tired.
H. S.	M	30	Tired past year.	20	66	100	In a few weeks increased energy.
H. H.	M	26	Exhausted all the time. Nervous past 1½ years.	30-40	90	108	In 2 weeks felt well; gained weight.
N. S.	F	21	Tired most of the day.	10-15	100	140	In 3 weeks felt well; gained 5 pounds.
B. R.	M	45	Fatigue. No relief from tonsillectomy, sedatives, tonics.	25	84	102	In 2 weeks increase in energy; gained 5 pounds.

In addition to these 2, 4 other patients whose main symptom was a tired feeling were relieved by stopping tobacco (Table 1). It is not meant to convey the impression that all patients who are tired and who smoke are improved by discontinuing the smoking. It is only meant to emphasize the point that there are people in whom fatigue is the result of cigarette smoking.

This brings up the question as to the products of tobacco smoke which are harmful to the system and especially what part of the smoke produces the general effects such as fatigue.

Dixon,⁸ in a very exhaustive study of tobacco smoke, has shown that the main constituents of the tobacco smoke are pyridine and its bases, ammonia, carbon monoxide and nicotine. Other substances present in traces are cyanides and sulphocyanides. Arsenic is present in American tobaccos in amounts many times greater than those permitted in foods.

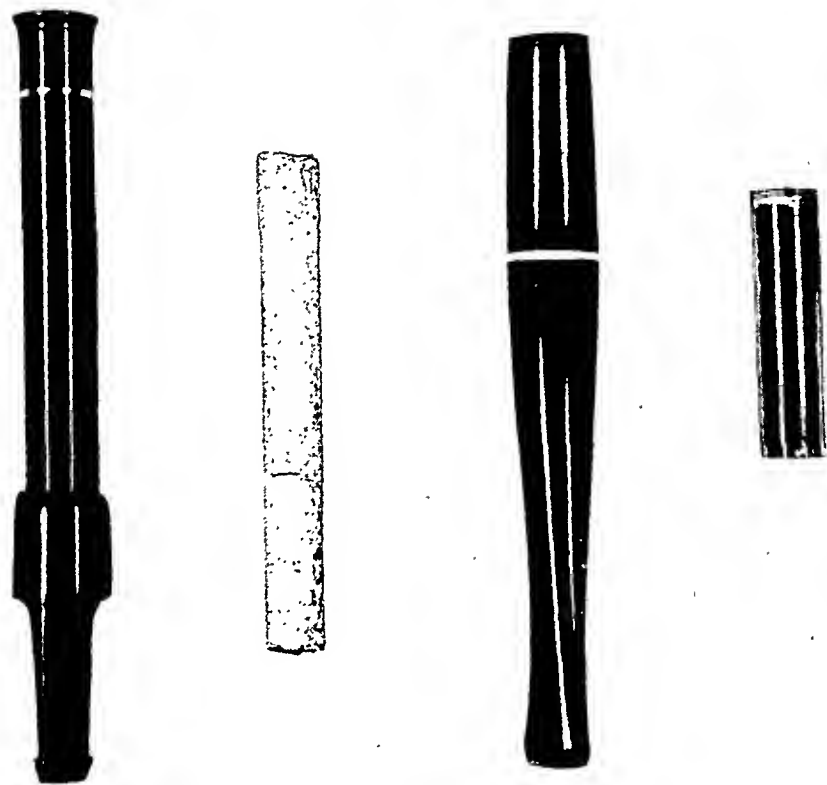


FIG. 1.—*A*, Zeuss type of filter holder. Cigarette used as the filter. *B*, Denicotea type of filter holder. Cartridge containing silica gel used as the filter.

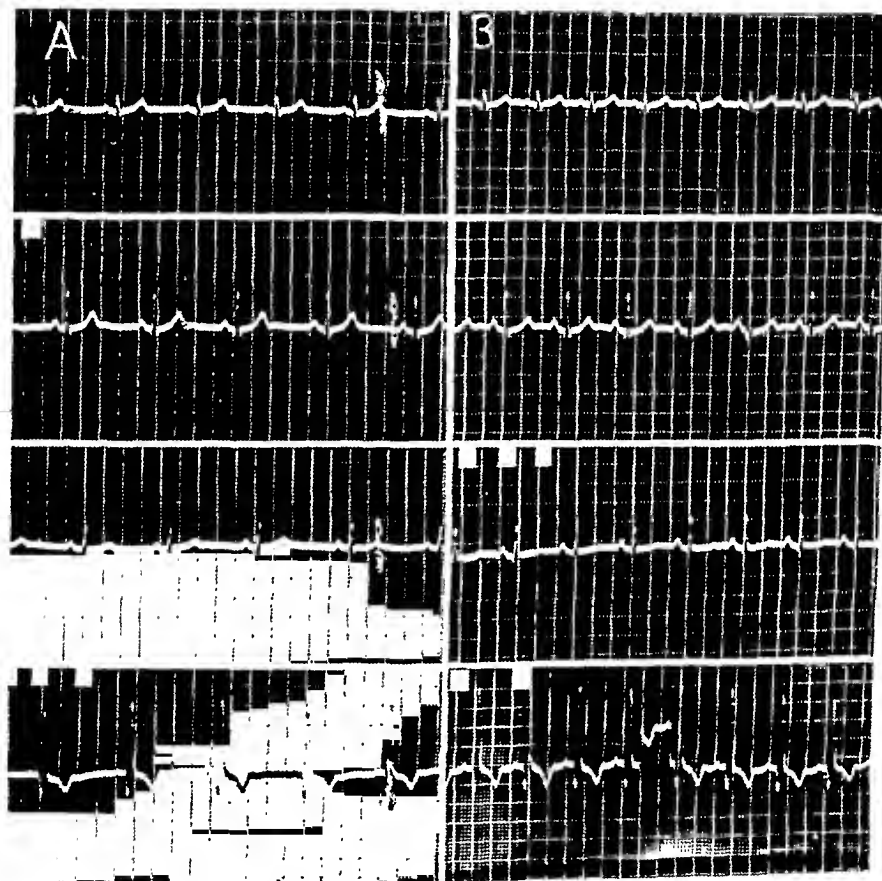


FIG. 2.—*A*, Electrocardiogram before smoking. *B*, Electrocardiogram after smoking one-half of a standard cigarette. Major effects, heart rate increased from 70 to 100; height of *T* waves decreased.

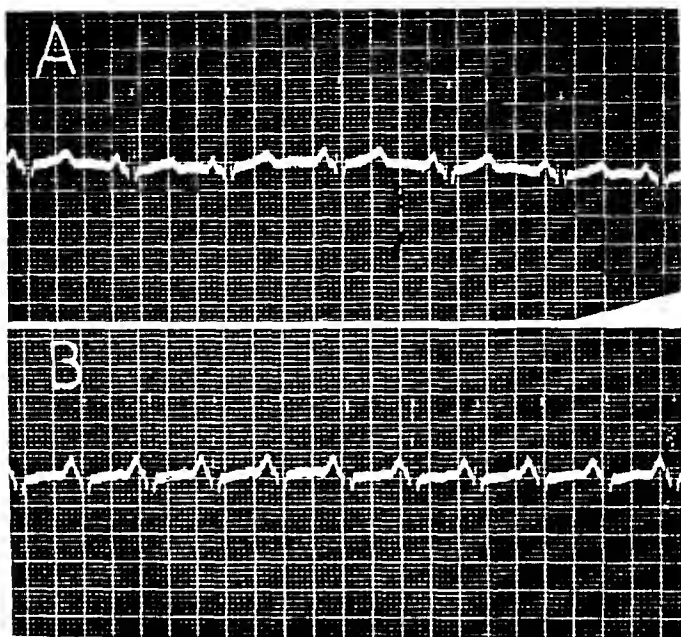


FIG. 3.—*A*, Lead II before smoking. *B*, Lead II after smoking one-half of a standard cigarette with the Zeuss filter. Major effects, heart rate increased from 100 to 130; *T* waves isoelectric.

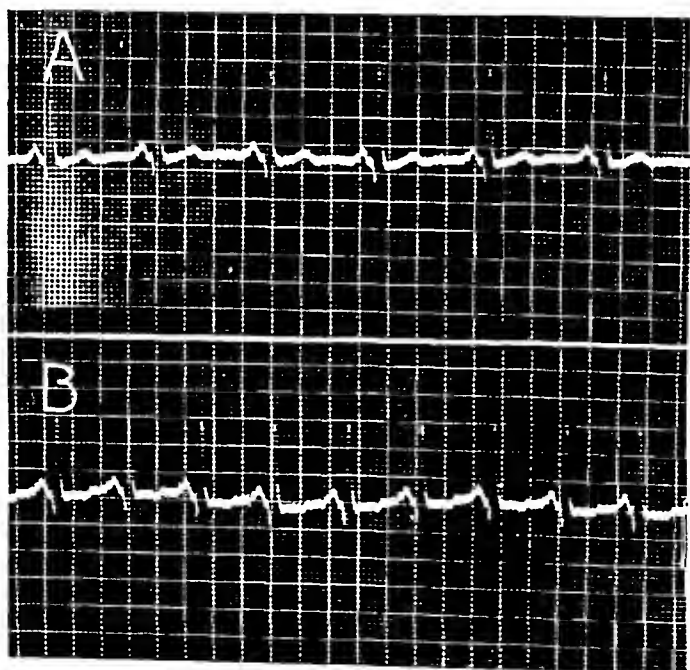


FIG. 4.—*A*, Lead II before smoking. *B*, Lead II after smoking one-half of a standard brand cigarette with the Denicotea filter. Major effects, heart rate increased from 84 to 120; height of *T* waves decreased.

FIG. 5

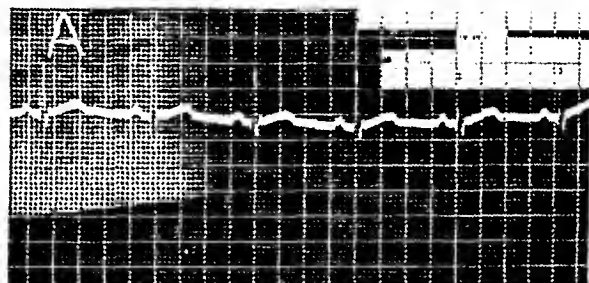
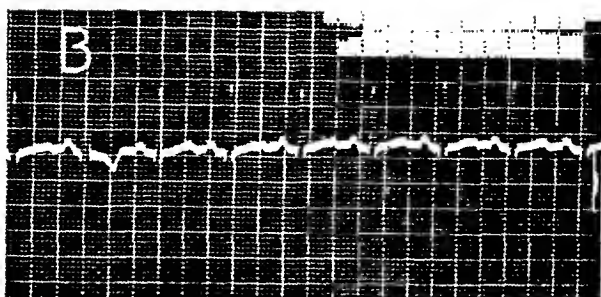


FIG. 6

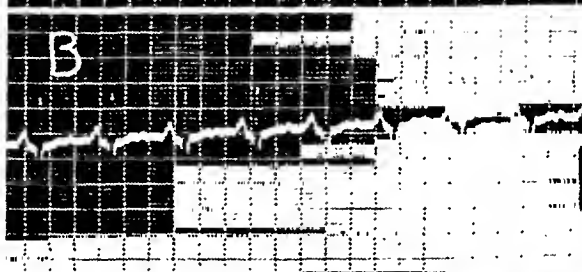
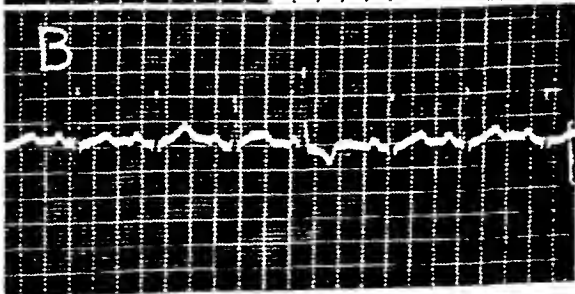
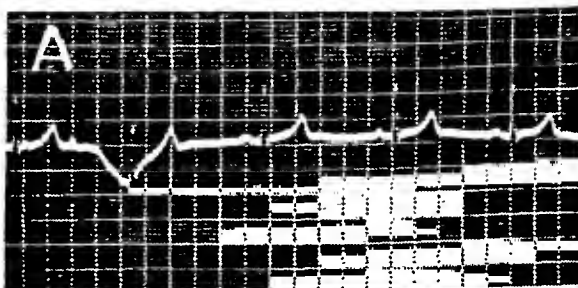


FIG. 7



He divided the effects of tobacco smoke upon the body into local and general. The ammonia gas and pyridine or pyridine derivatives produce the symptoms because of their irritation of mucous surfaces. It is these substances that cause the morning cough, the irritation of the throat and tongue, and conjunctivitis. He has shown that carbon monoxide and nicotine are the substances that can be absorbed into the circulation by way of the respiratory tract and it is these that can produce the general or systemic effect.

Cigarette smoke yields from 0.5 to 1% of carbon monoxide. The smoke from a pipe yields 1%, and that from a cigar 6 to 8%. The tobacco smoke reaches the mouth freely diluted with air and the amount of carbon monoxide absorbed in the mouth is negligible, so that pipe or cigar smokers who do not inhale have little to fear from carbon monoxide. Baumberger^{3a} has computed that cigarette smoke as it reaches the mouth may contain as much as 7.2 to 25 parts of carbon monoxide in 10,000 parts of air. This smoke if inhaled for 1 hour at the rate of 5 puffs a minute, theoretically could be enough to saturate the blood with 22% of carbon monoxide. But smokers do not habitually inhale as often or as continuously as this and Baumberger believes that it is extremely unlikely for the carbon monoxide to reach a sufficient saturation to produce any injurious effect in the average smoker. Thus by and large the systemic effect of carbon monoxide in tobacco smoke is negligible.

This leaves nicotine, the most important constituent of tobacco smoke, to produce a systemic effect. Various investigators^{8,11,14,19,20} have shown that nicotine is the substance that produces the general reaction from smoking. These general effects of nicotine will result in a rise in pulse rate, blood pressure and decrease in skin temperature. Realizing that nicotine is the harmful element in cigarette smoke and that in most people the habit is difficult to stop, the question arose as to the least harmful way of smoking.

At this time two filter holders appeared on the market, called Zeuss and Denicotea (Fig. 1), the use of which were supposed to remove a large percentage of the nicotine as well as the irritant products of cigarette smoke. It was wondered whether such filters would be effective in removing the nicotine effect and thus the harmful result of smoking.

For purposes of this study it was thought that some of the effects of the nicotine in the tobacco smoke could be best recorded by the electrocardiogram. The change in heart rate has been shown to be one of the most characteristic reactions of the nicotine of tobacco smoke and the electrocardiogram offers a permanent record. At the same time any other effect that smoking may produce on the electrocardiogram could be studied.

Method. The subjects tested did not smoke after the previous night. After resting comfortably in a chair, standard electrocardiograph tracings were taken before and after smoking one-half of the cigarette. It was noted

that the effect would occur within a minute after beginning to smoke, *i. e.*, even before one-quarter of the cigarette was consumed. As it was also observed that the information desired could be obtained for all practical purposes from the comparisons of Leads II before and after smoking, this was the lead that was studied in most of the tests. With this technique tracings were taken before and after smoking standard and denicotinized brands of cigarettes. Then on different days or with different subjects using the same technique the effect of smoking the same kind of cigarettes with a holder containing a filter was noted. The observation whether the subject puffed or inhaled was also made.

The filters used in this study, as already stated, are on the market under the name of Zeuss and Denicotea (Fig. 1). The Zeuss Filter-Holder consists of an aluminum tube in which a cigarette is placed to act as a filter. The Zeuss corporation claim that over 70% of the nicotine and tar are removed from the cigarette smoke by this method. In addition, they tell you to smoke all you like.

The Denicotea Filter-Holder consists of a tube in which is inserted a cartridge containing a silica gel to act as the filter. This filter has been examined by the Chemical Laboratory of the American Medical Association^{1b} and their report has shown the presence of silicic acid in the granular material in the filter. After smoking, qualitative tests of the filter have revealed the presence of nicotine, traces of cyanides, pyridines and resinous material. Their conclusions are that this filter removes 60% of the nicotine from the cigarette smoke and that its efficiency decreases with its use. Cyanides, pyridine and some of the resinous material also are removed from the smoke by this filter.

TABLE 2.—THE EFFECT OF CIGARETTE SMOKING ON LEAD II OF THE ELECTROCARDIOGRAM.

Age groups.	No. of tests.	Sex.		Increase in heart rate.			Decrease in height of T wave in millimeters in Lead II.		
		M.	F.	No. tests with no increase.	High-est.	Aver.	No. tests with no decrease.	Low-est.	Aver.
17-35 . . .	44	14	30	3	50	21	10	3	0.78
35-50 . . .	9	5	4	2	40	18	7	1	0.51
50-on . . .	11	6	5	7	16	4	8	0.75	0.12
Total . . .	64	25	39	12	25		

Data. Table 2 is a summary of the effect of smoking cigarettes on Lead II of the electrocardiogram. There were 64 tests made, 25 males and 39 females. These 64 subjects were divided into three age groups; the young consisted of subjects between the ages of 17 and 35; the middle age group between the ages of 35 and 50; the old age group from 50 upwards. The number of cases with no change in heart rate, the maximum and average increase in heart rate as well as changes in the T wave were recorded. In the young group there were 44 tests, only 3 of whom had no increase in heart rate after smoking. The highest increase in rate was 50 per minute; the average for this group was 21.

In this same group, changes in the *T* wave took place in 34 of the 44 subjects, the greatest drop was 3 mm. and the average was 0.78 mm.

In the middle age group the figures were comparable, but in the group over 50 years of age there was no increase in heart rate in 7 out of the 11 tested; the highest increase was 16 and the average increase was only 4 beats per minute. Likewise changes in the *T* wave were less significant.

TABLE 3.—COMPARISON OF THE EFFECT OF SMOKING STANDARD AND SO-CALLED DENICOTINIZED BRANDS OF CIGARETTES ON LEAD II OF THE ELECTROCARDIOGRAM.

Age group.	Standard brands.									Denicotinized brands.								
	Total No. of tests.	Sex.		Increase of heart rate.			Decrease of height of <i>T</i> in Lead II.			Total No. of tests.	Sex.		Increase of heart rate.			Decrease of height of <i>T</i> in Lead II.		
		Male.	Female.	No. tests with no change.	Highest.	Average.	No. tests with no change.	Lowest.	Average.		Male.	Female.	No. tests with no change.	Highest.	Average.	No. tests with no change.	Lowest.	Average.
17-35	27	11	16	3	45	23	7	3.0	0.65	17	3	14	0	50	16	3	3.0	0.69
35-50	8	5	3	2	38	17	5	1.0	0.15	1	0	1						
50-on	10	5	5	6	16	4	7	0	0	1	1	0						
Total	45	21	24	19	4	15						

Table 3 is a comparison of the results obtained from the standard brands of cigarettes in which the nicotine contents averages about 2% as against the so-called denicotinized brands in which the nicotine content has been estimated to give an average of about a little less than 1%.¹ The standard brands of cigarettes mainly used were Chesterfield, Camel and Lucky Strikes. The denicotinized brands consisted of Sano and Carl Henry.

In the young group, there were 27 tests with standard brands as compared with 17 subjects in the denicotinized brands. Three of the subjects smoking standard brands failed to get a rise in heart rate while every one of the 17 tests in the denicotinized group had a rise in rate. The highest rise in the heart rate was 45 in the standard brands as compared to 50 in the denicotinized. The average was 23 in the former as compared to 16 in the latter. *T* wave changes were comparable in both types of cigarettes. Not enough tests were made in the older groups to be of any significance.

Table 4 is a chart comparing the effects of smoking cigarettes of both brands without a filter as compared to smoking with both the Zeuss and Denicotea types of filters. Here the results in people under 50 are compared. Briefly, the standard brands with no

filters showed an increase in the heart rate in 14 of the 18 subjects tested as compared to an increase in the rate in all cases with the Zeuss filter and an increase in 7 of the 8 subjects smoking with a Denicotea filter.

The findings are comparable for the changes in the *T* waves and more details can be obtained from studying the tables.

TABLE 4.—COMPARISON OF SMOKING STANDARD AND SO-CALLED DENICOTINIZED CIGARETTES WITH AND WITHOUT FILTERS ON LEAD II OF THE ELECTROCARDIOGRAM.

Age group:	Standard brands.									Denicotinized brands.								
	No filter.			Zeuss filter.			Denicotea filter.			No filter.			Zeuss filter.			Denicotea filter.		
	17-35 yrs.	35-50 yrs.	Total.	17-35 yrs.	35-50 yrs.	Total.	17-35 yrs.	35-50 yrs.	Total.	17-35 yrs.	35-50 yrs.	Total.	17-35 yrs.	35-50 yrs.	Total.	17-35 yrs.	35-50 yrs.	Total.
No. of tests . . .	14	4	18	6	3	9	7	1	8	3	1	4	10	0	10	4	0	4
No. of tests with no increase in heart rate .	3	1	4	0	0	0	0	0	0	0	0	0	1	..	1	1	..	1
Highest increase in heart rate	40	38	40	45	18	45	40	30	40	50	36	50	30	..	30	30	..	30
Average increase in heart rate	19	14	16	30	15	25	24	34	21	22	36	21	13	..	13	17	..	17
No. of tests with no decrease in height of <i>T</i> wave	5	3	..	2	2	4	3	..	3	1	1	2	4	..	4	1	..	1
Lowest decrease in height of <i>T</i> wave	1.5	0.5	..	3.0	0.5	3	1.5	..	1.5	3.0	..	3.0	3.5	..	3.5	1.25	..	1.25
Average decrease in height of <i>T</i> wave	0.42	0.12	..	1.12	0.16	0.91	0.57	..	0.50	1.33	..	0.8	0.55	..	0.55	0.56	..	0.56

TABLE 5.—COMPARISON OF THE EFFECT ON THE ELECTROCARDIOGRAM OF INHALING VERSUS PUFFING IN CIGARETTE SMOKING IN PEOPLE UNDER FIFTY.

	No. tests.	Increase in heart rate.			Decrease in height of <i>T</i> wave.		
		No. tests with no change.	Highest.	Average.	No. tests with no change.	Lowest.	Average.
Inhale	59	4	50	19	22	3.0	0.64
Puff	5	2	20	4	3	0.5	0.20

Table 5 demonstrates the effect of inhaling *versus* just puffing. In the latter, only the mucous membrane of the mouth is available for absorption. From this table it can be readily seen that most of the cigarette smokers inhaled. The 5 that puffed had an increase in pulse rate in 3 cases, the highest being 20 as compared to 50 in those who inhaled, with an average rate increase of 4 as compared to 19 in the subjects who inhaled.

Figures 2 through 7 demonstrate the effect of inhaling cigarette smoke on Lead II of the electrocardiogram. Figure 2 also shows the effect on the other leads.

Figure 2 represents the 4 leads of the electrocardiogram taken after smoking one-half of a standard brand of cigarette. The heart rate has increased from 80 to 100 and the *T* wave has dropped 1 mm.

Figure 3 shows Lead II before and after smoking one-half of a standard brand of cigarette with the use of a Zeuss filter. Here the rate has increased from 100 to 130 and the *T* wave has become flat. This figure also shows one of the minor and less consistent changes, namely, a slight increase in the height of the *P* wave.

Figure 4 reveals Lead II before and after smoking one-half of a standard brand of cigarette with the use of a Denicotea filter. These leads show a rise in heart rate from 84 to 120 and a flattening of the *T* wave. One of the minor changes also noted is a decrease in the amplitude of the *QRS* complex.

Figure 5 represents Lead II taken before and after smoking one-half of a denicotinized brand of cigarette. The heart rate has increased from 70 to 110, the *T* wave has decreased about 3 mm. A minor change here is the increase in the height of the *P* wave and the amplitude of the *QRS* complex.

Figure 6 shows the effect of smoking a denicotinized cigarette with a Zeuss filter. The heart rate has increased from 70 to 110, and the *T* wave has become isoelectric. The *P* wave has increased about 1 mm.

Figure 7 demonstrates the effect of smoking one-half of a denicotinized brand of cigarette with a Denicotea type of filter. The heart rate has increased from 60 to 100 and the *T* wave has dropped 3 mm. The *P* wave is slightly more prominent after smoking.

These figures definitely show increases in heart rate and lowering of the *T* waves as well as minor changes in the *P* waves and amplitude of the *QRS* complex after smoking standard and denicotinized brands of cigarettes. It is readily seen that similar results occurred with both brands of cigarettes with and without the use of filters.

Discussion. Dixon,⁸ as already mentioned, has reviewed the whole tobacco question and Bastedo² more recently has mentioned the various systemic symptoms that can result from smoking. The evidence that the nicotine of the tobacco smoke is the cause of these symptoms has been proved by numerous studies.^{8,11,14,20} Baumberger^{3b,c} in 1923 has demonstrated that the nicotine content of cigarette smoke is about 0.57% of the weight of the cigarette tobacco; 14 to 33% of this nicotine appears in the smoke puffed. He further has shown that 66.7% of the smoke and presumably the nicotine is retained in the body in puffing, while 88.2% is retained in inhaling. Maddock and Coller,¹⁴ stating that a standard brand of cigarette contains about 1 gm. of tobacco and that about 2.2% of this is nicotine, have calculated that in puffing two-thirds of a cigarette the body will absorb 2.52 mg. of nicotine and that in inhaling the same amount of cigarette smoke, 3.33 mg. of nicotine will be absorbed. The intravenous injection of 1 mg. of nicotine will produce

an increase in blood pressure, pulse rate and decrease in the skin temperature of the fingers and toes.¹⁴ On smoking a cigarette these same effects will occur. Thus these results following smoking is due to nicotine.

Tournade, Chevillot and Bernot,¹⁹ by comparing the effect of nicotine and the inhalation of tobacco smoke on denervated tongue muscle, also have shown that nicotine is the substance present in the tobacco smoke that causes the systemic effects.

The effect of tobacco smoking on the electrocardiogram has been reviewed recently by Graybiel, Starr and White.⁹ They mention the studies of Bull, Clerc and Pezzi,⁶ and Mattioli¹⁵ who studied the effect of nicotine in animals by the use of the electrocardiogram. The former workers observed nodal rhythm, auricular flutter and heart block after the injection of toxic doses of nicotine in dogs and rabbits.

Ssalischtscheff and Tschernogoroff^{17a,b} also reviewed by Graybiel and his collaborators,⁹ were the first to analyze the effect of inhaling tobacco smoke on the human electrocardiogram. In their first article^{17a} they worked with rabbits under ether narcosis and they noted that it required the injection of 0.1 mg. of nicotine to produce a slowing of the rhythm. In their work on humans^{17b} they took electrocardiograms every 5 to 10 minutes until toxic symptoms of smoking occurred. They found that at the height of intoxication the heart rate was accelerated except in 1 instance. In most of their cases the form and height of the electrocardiogram did not change with the toxic symptoms from smoking.

Graybiel, Starr and White⁹ noted in their study that after smoking a cigarette, or after toxic symptoms such as dizziness appeared, there was an average increase in heart rate of 13 a minute and that lowering or inversion of the *T* waves took place in 15 of the 45 subjects tested. Minor changes occurred in the *P-R* interval and the amplitude of the *QRS* complex in a few cases. They noted that full atropinization produced changes in the electrocardiogram similar to those from smoking.

Knowing that cigarette smoke may produce an increase in the heart rate as well as a decrease of the *T* wave and other minor changes in the electrocardiogram and knowing that nicotine is the factor in the cigarette smoke that produces these effects, we are justified in using the electrocardiogram to determine the efficiency of filters in removing the nicotine effect of smoking various brands of cigarettes.

In our study, it has been conclusively shown that smoking one-half of a cigarette produces a definite effect on the electrocardiogram in a large majority of subjects under 50; and that this effect was mainly registered by an increase in the heart rate and a decrease in the height of the *T* waves. In some cases there were an increase

in the height of the *P* wave and minor changes in the amplitudes of the *QRS* complex.

From studying the charts in similar age groups the effect from smoking standard and denicotinized cigarettes is very similar both in increase in rate and in lowering of the *T* waves. Again, smoking with the use of a filter produces the same effect on the electrocardiogram as the unfiltered smoke.

What is the significance of all this?

First, it seems that people under 50 reacted almost consistently to cigarette smoking as far as the heart rate goes. Those over 50 responded to a lesser degree if at all to cigarette smoking.

The action of nicotine is one of stimulation of the entire nervous system and this is followed by depression. The time the stimulation lasts usually coincides with the absorption of the nicotine, that is, with the period of active smoking. The stimulation of the sympathetic causes contraction of the arteries as shown by a decrease in skin temperature.¹⁴ Contraction of the arteries alone can be the cause of the increased heart rate in order to obtain the same volume output per minute although direct action on the sympathetic to the heart may play the main part in the increased rate.

In people over 50 the arteries may not be elastic enough to respond to this stimulation, or the mucous membrane of the respiratory tract in the older people may not absorb the nicotine as readily. This point could be determined by the comparison of the effect of nicotine injected intravenously and that from smoking. Another point noted was that the 3 subjects in the group under 50 who failed to respond were not totally normal people. One had an essential hypertension, one ulcerative colitis and one mucous type of colon with achlorhydria. This may point to the fact that in the case of hypertension, overactivity of the sympathetic nervous system was already present. In the latter 2 cases it may be due to poor absorbability of the mucous membranes. These points will be elucidated by further study of such cases.

Sharlit¹⁶ in 1935 suggested that a filter could remove the combustion products from the smoke stream and believed that such a substance was available but did not mention the name. By this method he suggested that the health hazard of cigarette smoking could be removed. Apparently the present filters on the market, notably the Zeuss and Denicotea types already described, do filter out a large percentage of nicotine as well as the substances that produce local irritation. But this study shows there is still enough nicotine in the filtered smoke that enters the mouth to produce a definite nicotine reaction. Although these filters are probably valuable by removing a part of the products that cause the local irritation of smoking, they have very little or no value in avoiding that which produces the systemic and habit effect of smoking,

namely the effect of nicotine. It may be suggested that although some nicotine gets through the filters, there is less nicotine to produce harmful effects. But the answer to this is that nicotine is a very toxic drug and it only requires 1 mg. to produce the specific effect. If in inhaling the smoke of two-thirds of a cigarette 3.33 mg. of nicotine are absorbed,¹⁴ there still will be absorbed about 1 mg. of nicotine even after 70% of this nicotine is removed by a filter. But as the American Medical Association¹⁵ report shows 60% is the highest efficiency of the new cartilage in the Denicotea filter and it decreases with each smoke, more than 1 mg. will be absorbed with this filter; more than is required to get a systemic effect. Even puffing, as tested with 2 people using a Zeuss filter, allowed enough nicotine into the mouth to get an increase in the heart rate. This demonstrated how readily nicotine causes these responses.

What is the mechanism that produced the fatigue from cigarette smoking? Although Dill and his collaborators⁷ have reported that smoking 1 cigarette produces no change in the blood sugar the consensus of workers indicates that cigarette smoking produces a rise in blood sugar.^{10,13,18}

McCormick¹³ believes that the rise in blood sugar due to smoking is a protective mechanism as it occurs after morphine, strychnine and other drugs, as well as in infectious diseases. This rise in blood sugar depletes the glycogen stored in the muscles and this depletion represents a loss of potential muscular energy. Thus it can be readily seen that repeated cigarette smoking continues to deplete this muscle glycogen leaving a fatigued individual. He gives definite experimental evidence to prove this point. That smoking can cause fatigue has been shown by Baumberger and co-workers^{4,5} who mention Lee's experience.¹²

The changes in *T* wave in the electrocardiograms observed from smoking in this study do not necessarily mean that there is coronary insufficiency but probably represents a reaction of the heart to increased work, as suggested by Graybiel and collaborators.⁹ Even though these changes do not mean coronary spasm, yet the increased heart action, without the benefit to the body as a whole that healthful exercise produces, can do no good and probably does harm over a period of time.

LEGENDS FOR FIGS. 5, 6 AND 7.

FIG. 5.—*A*, Lead II before smoking. *B*, Lead II after smoking one-half of a denicotized cigarette. Major effects, heart rate increased from 70 to 110; height of *T* waves decreased 3 mm.

FIG. 6.—*A*, Lead II before smoking. *B*, Lead II after smoking one-half of a denicotized cigarette with the Zeuss filter. Major effects, heart rate increased from 70 to 110; height of *T* waves lowered 1 mm.

FIG. 7.—*A*, Lead II before smoking. *B*, Lead II after smoking one-half of a denicotized cigarette with the Denicotea filter. Major effects, heart rate increased from 60 to 100; height of *T* waves decreased 3 mm.

Summary. 1. Six cases, whose main symptom was a fatigue that was relieved by discontinuing smoking, are summarized. The mechanism of the cause of fatigue is discussed.

2. The effect of smoking standard and denicotinized cigarettes with and without filters on Lead II of the electrocardiogram is demonstrated and discussed.

Conclusions. Cigarette smoking can be the cause of fatigue in some people and this fatigue can be relieved by stopping cigarette smoking.

Cigarette smoking produces definite changes in the electrocardiogram, mainly: *a*, An increase in the heart rate; *b*, a lowering of the *T* wave.

Both standard and the so-called denicotinized brands produce the same effects.

Although the filter-holders described decrease the amount of nicotine in cigarette smoke, a sufficient amount of nicotine is still available to produce the above changes in the electrocardiogram.

These effects occur mainly in people under 50 years of age.

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BOOK REVIEWS AND NOTICES.

THE TROUBLED MIND. A Study of Nervous and Mental Diseases. By C. S. BLUEMEL, M.A., M.D., F.R.C.P., M.R.C.S. (ENG.). Pp. 520. Baltimore: The Williams & Wilkins Company, 1938. Price, \$3.50.

In plain language, the author discusses such ramifications as neuro-psychiatry may have in the realms of religion, crime, business, advertising, politics, peace and war, together with some original theories pertaining thereto; and that is a rather large order. The subject-matter is considered under the following headings: Fixed ideas and reactions; psychoneurosis—its manifestations; psychoneurosis—its nature and causes; traumatic hysteria; clinical types of inhibition; sundry disorders; mental illnesses; closing comments. Many short histories well illustrate the differences between harmless mental subjects and those that are public disturbers.

Nearly half of the space is devoted to manifestations, nature and causes of the psychoneuroses; that is, those functional nervous disorders characterized by emotional and physical disturbances. Their "therapy may include such technique as persuasion, suggestion, desensitization, psycho-catharsis, hypnosis, psychoanalysis, distributive analysis, unconditioning, and so on; . . . the objective is that of establishing emotional flexibility." There are minor errors, such as, traumatic hysteria which should be post-traumatic hysteria; that severe melancholia is closely allied to dementia precox is an opinion not usually held; nor is there "softening of the brain" in paresis. Being free from commercialism and unnecessary sex discussions, this wholesome book may be recommended to the lay reader. The bibliography is scant, a glossary is appended and there is an informative index.

N. Y.

RECENT ADVANCES IN PATHOLOGY. By GEOFFREY HADFIELD, M.D., F.R.C.P. (LOND.), Professor of Pathology in the University of London; Pathologist to St. Bartholomew's Hospital, etc., and LAWRENCE P. GARROD, M.A., M.D., B.CH. (CAMB.), F.R.C.P. (LOND.), Professor of Bacteriology in the University of London; Bacteriologist to St. Bartholomew's Hospital, etc. Pp. 420; 65 illustrations. Third Edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1938. Price, \$5.00.

Now that the volumes of this useful series are appearing in various editions, it should be noted that a later edition does not bring merely the knowledge acquired since the previous edition, as in a Year Book; but that it is a revised version of the earlier edition. Thus in this volume "little more than half of the previous text is retained. The first chapter is entirely new, and deals with two aspects of the fundamental problem of resistance to infection. One of these is concerned with the nature and significance of bacterial allergy, and adequate treatment of this subject has also necessitated re-writing sections on the pathogenesis of rheumatic fever, lobar pneumonia and glomerulonephritis. In the third chapter, which is also entirely new, we have stressed the striking potentialities of undifferentiated mesenchyme and have attempted to summarize present knowledge with regard to the reticuloses and the reticulo-sarcomata. Other chapters in which there are extensive alterations are those on deficiency diseases and on cancer. . . . Extensive additions have also been necessary in connection with subjects of silicosis, gastritis, the relationships between gastro-intestinal

function and anemia, and disorders of the adrenal and pituitary glands. In order to make further room for new matter, two chapters and five sections on subsidiary subjects have been omitted, as has a good deal of introductory matter originally designed to enable the reader to view the subject in its proper relationship to others. Only those who have attempted the compilation of a work of this scope and function can appreciate the difficulty of deciding what to include and what to omit." Nevertheless, with due regard for the differences in British and American requirements, we believe that the authors have acquitted themselves well. E. K.

A GENERAL TEXTBOOK OF NURSING. A Comprehensive Guide to the Final State Examinations. By EVELYN C. PEARCE, Sister Tutor, The Middlesex Hospital, etc. Pp. 888; 176 illustrations. New York: E. P. Dutton & Co., 1938. Price, \$3.75.

THIS book is written to serve as an introduction to nursing for the student nurse. Though written simply and briefly, nothing is sacrificed that would be of value to the student as she travels from one department to another in the hospital.

In many treatments administered by doctors, just what is expected to occur is described graphically, in order that the nurse may see the reason for supplying necessary equipment. It is interesting to discover the use of different materials. For instance one learns that salt may be used on ice for ice bags; small ice packs can be made of gutta percha; tow may be used for wash cloths. In England wool and tow take the place of our cotton. The measuring system is more exact—one computes dosage on the basis of 110 minims to 100 grains. Many unfamiliar terms are used and it will add considerably to one's vocabulary if a dictionary is handy.

One thing that might be added to the book is a paragraph or more on artificial respiration. Neither the respirator that we use in the treatment of respiratory paralysis nor the use of the oxygen tent or chamber in oxygen therapy is mentioned, although complete directions with illustrations are given for administering the oxygen by nasal catheter.

However, the book contains a great amount of material with illustrations of charts, trays, and so on., that make it important for the reference library and for anyone to own who has need for information regarding nursing in a brief but accurate detail.

Very few textbooks are able to convey to the reader a sense of the spirit back of nursing that transforms simple tasks into a work of art. But it is just such features that bring a picture of a work that is full of life and spirit; "He can then be put to bed and should be given a hot drink and tucked up and made to feel happy, cheerful and contented as he looks forward to his future treatment."

Surely nurses everywhere should be proud of this book and although it may seem lengthy, it should be very profitable and enjoyable to anyone interested in actual bed-side nursing. M. S.

THE PATHOLOGY OF DIABETES MELLITUS. By SHIELDS WARREN, M.D., Pathologist to the New England Deaconess, The New England Baptist, The Huntington Memorial, and the Pondville State Hospitals; Director of Massachusetts State Tumor Diagnosis Service; Assistant Professor of Pathology in the Harvard Medical School, Boston. With a Foreword by ELLIOTT P. JOSLIN, M.D. Pp. 246; 86 illustrations and 3 colored plates. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, \$4.75.

THE eight years that have elapsed since the appearance of the first edition of this work have been rich in diabetic study, much of which affects

some phase of the subject considered here. The preservation of diabetic lives with improved use of insulin, and especially of protamine insulin, has emphasized such problems as the sclerosis of arteries (especially of the heart and legs), effects of insulin overdosage, surgical operations and so on. As in the first edition, pathologic physiology is properly emphasized, while the great amount of biopsy material, on which the pathologic anatomy is considerably based, reminds that here the living, as well as "mortui, vivos docent." The colored illustrations are excellent; this cannot be said of many of the black and whites.

E. K.

DISEASES OF WOMEN. By Ten Teachers, under the Direction of CLIFFORD WHITE, M.D., B.S. (LOND.), F.R.C.P. (LOND.), F.R.C.S. (ENG.) F.C.O.G. Edited by SIR COMYNS BERKELEY, CLIFFORD WHITE and FRANK COOK. Pp. 492; 159 illustrations and 7 colored plates. Sixth Edition. Baltimore: William Wood & Co., 1938. Price, \$6.00.

THIS manual on gynecology written by 10 English teachers of the subject, is a fine example of collective authorship. The subject matter presents the major headings concisely for the benefit of the student and yet there is sufficient emphasis on treatment to make the book particularly applicable to the practitioner. In the revision of this sixth edition, the sections on physiology and disorders of menstruation have been completely rewritten to bring it abreast of the present day ideas and advances. It is interesting that the chapter on radiology in earlier editions has been dropped. There has been added to those sections where radiation should be useful in treatments of the disease discussed a detailed description of the appropriate radiological methods. Without going into ethical or sociological indications for birth control the methods of contraception and of sterilization form the text of a new and well written chapter. There is a marked increase in the number of illustrations, particularly as regards histology.

This book may be regarded as an authoritative presentation of present day gynecological teaching and practice in England.

P. W.

MEDICAL JURISPRUDENCE AND TOXICOLOGY. Edited by JOHN GLAISTER, M.D., D.Sc., Barrister-at-Law, Regius Professor of Forensic Medicine, University of Glasgow, etc. Pp. 747; 107 illustrations and 8 plates. Sixth Edition: Baltimore: William Wood & Co., 1938. Price, \$8.00.

In this edition less emphasis is placed on small-type interpolations. New material includes dermal and palmar prints, maggots, the Ruston Case, blood-grouping, seminal fluid grouping, war gases and so on.

E. K.

HUMAN POWERS AND THEIR RELATIONS. By K. W. MONSARRAT. Pp. 289; 60 figures. London: Hodder & Stoughton, Ltd., 1938. Price, 10/6.

THE material of this interesting book by an English biologist is obviously arranged with great care to make the sequence of ideas both clear and logical. After an orienting preface and a chapter of summary, placed at the beginning rather than the end of the book, the author proceeds to discuss the process of knowing and formation of ideas, then their relation to observed physical phenomena, biological phenomena from the simplest bacteria to the human being, and finally the conditions for equilibrium and freedom in man's social relations, with a comment on these relations in Britain at the present time. Any reproduction of the author's thesis in a review of this length must be extremely curtailed, but very briefly the propositions are these:

1. That knowing should be conceived as a process, definable only in terms of what it does: the production and presentation of reports, which may be itemized as ideas (p. 20).

2. That the self-derived idea "power-to-do" is given, primary and fundamental, it being the one idea irreducible to any terms but its own (p. 20).

3. That there is a duality in the relations of the process knowing. Those ideas (of the self) in which no "sensuous transactions" can be traced—*e. g.*, power, unity, enduring—are termed "identifications;" those ideas (of the whole world) in which sensuous transactions can be traced are termed "images" (p. 29).

4. That according to the proper use of ideas the world is to be conceived as occupied and wholly constituted by items of "power." The conception of items of "matter" is due to the duality of the knowing process, not to any duality belonging to the world itself (p. 20).

5. That much of the world is made up of groups of "power items," each group persisting through the mutual compensation without fusion of the power-items, and through the balancing contributions between the whole assembly and all the surrounding influences (p. 20).

6. That all action everywhere and at all times is interpretable as action toward an equilibrium (p. 21).

7. That the structure-integration of assemblies varies in complexity, different planes thereof being conceivable. The human being is to be conceived as an example of an influence-assembly, the human social group as an assembly in the making (p. 21).

8. That the ready maintenance of balance on one level involves the availability (freedom) of influence for the creation of balance-relation on a further level (p. 21).

9. That the conditions which govern the stability of assemblies in general, and their freedom for creating new relations, are discernible (p. 21).

The chief criticism which can be made of this thoughtful work is not so much of its content as of the implications and manner of its presentation. The author refers to his method of approach to these problems as "the historical method," apparently implying that it is original with him, and contrasts it with the "scientific" and "philosophical" methods, which he reproaches the one for "its peculiar interpretation of images as images of matter," and the other for "its abstraction and neglect of sensuous analysis and image-forming." Actually there is no essential difference between science's mechanical image, with its items of matter and their cause-effect relationships on the one hand, and the author's dynamic image, with its power-items and their "contribution" relationships on the other hand. Science does not concern itself with the corporeal nature of these items of matter, but with their individuality and relationships: according to Hobbes, a contemporary of Galileo, phenomena are, in their essence, motions, causes are the simple elements of motion, and effects are again motions. Also, it is far from true that philosophers have neglected sensuous analysis and image-forming; in the absolutely honest and consistent empiricism of David Hume, for example, there are many points of resemblance with the author's propositions, although Hume carries his idealism even further.

Enough has been given in the propositions outlined above to indicate that the author's detailed application of them to many biological and social phenomena are of absorbing interest to those having even a brief acquaintance with biology. In its construction and depth of thought this book is superior to many of the quasi-philosophical works of present-day physicists of otherwise good repute. A few of the propositions may be questioned; most of them are sound, although, as already stated, they are given in a misconception of the "scientific" and "philosophical" methods, and the insistence on a new set of names for what are really the same things is not neces-

sary. Fundamentally there is little that is new in the propositions. From statements made here and there in the book, including a penetrating one on the Heisenberg indeterminacy principle (physicists, please note) the author, while avoiding the terms mechanical and determined, apparently considers all world phenomena to be orderly and the order to be discernible, but the manner in which he unites the dual concepts of mind and matter into one of power-items is more reminiscent of the Leibnizian monad than anything else.

It is a pity that the author's apparent inadequate acquaintance with or inadequate comprehension of the history of philosophy should prove such a major defect in what is otherwise a work of deep, clear insight into problems which confront all scientists, whatever their field. R. S.

A TEXTBOOK OF HISTOLOGY. Functional Significance of Cells and Inter-cellular Substances. By E. V. COWDRY, Professor of Cytology in the School of Medicine, Washington University, St. Louis, Mo. Pp. 600; 323 illustrations, some in color. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, \$7.00.

PROFITING by help of "true friends" who offered suggestions for improvement over the first edition, the author has added to this edition a valuable introduction (partly historical) and many illustrations (especially to show normal variations and the effect of ageing). He has not acceded to criticism that the book assumes too much preliminary training. "To cater to the least informed members of the class is not our purpose. When we expect but little of the students we receive little in return." The final bibliography, extensive for a book of this sort, carries out this thought. E. K.

HANDBOOK OF PRACTICAL BACTERIOLOGY. A Guide to Bacteriological Laboratory Work. By T. J. MACKIE, M.D., D.P.H., Professor of Bacteriology, University of Edinburgh; Honorary Bacteriologist to the Royal Infirmary, Edinburgh, etc., and J. E. MCCARTNEY, M.D., D.Sc., Director of Researches and Pathological Services, London County Council, etc. Pp. 586. Fifth Edition. Baltimore: William Wood & Co., 1938. Price, \$4.00.

THE main virtue of this book lies in its elementary straightforwardness and clear description of technical procedures. While there are other works on bacteriological technique that are of more value to the advanced worker, this one is a very helpful guide for the routine worker and those not having an extensive bacteriological background.

A serious effort has been made to bring this edition up-to-date, but it seems to have been only partially successful. A few pages may include all of the latest information on a given subject, only to relapse on other pages into sections which are several years behind the times. Several important recent innovations have been completely overlooked. Nevertheless, because of its simplicity and fundamental directness of approach, this book may well be regarded as one of the "primers" of the routine laboratory.

D. L.

THE HARVEY LECTURES, SERIES XXXIII. Delivered under the Auspices of The Harvey Society of New York, 1937-1938. Under the Patronage of the New York Academy of Medicine. Pp. 275; 60 illustrations. Baltimore: The Williams & Wilkins Company, 1938. Price, \$4.00.

THIS 33d volume of the well-known Harvey Lectures contains the following lectures: The Nature of the Visual Process (Selig Hecht); The Pasteur-Meyerhof Reaction in Muscle Metabolism (Einar Lundsgaard); The Func-

tional Significance of the Lymphatic System (Cecil K. Drinker); Transfers of Water and Solutes in the Body (John P. Peters); Studies on the Cortical Representation of Somatic Sensibility (Philip Bard); The Isolation and Properties of Tobacco Mosaic and Other Virus Proteins (Wendell M. Stanley); The Chemistry and Biology of Male Sex Hormones (F. C. Koch); Experimental Hypertension Induced by Renal Ischemia (Harry Goldblatt). The usual high standard of this Series has been maintained.

E. K.

THE CHEMISTRY OF THE STERIDS. By HARRY SOBOTKA, Chemist to the Mount Sinai Hospital, New York. Pp. 634. Baltimore: The Williams & Wilkins Company, 1938. Price, \$8.50.

THIS is an excellent compilation of physical constants upon all the known derivatives of the sterols. Included in this class of chemical compounds are the bile acids, the antirachitic vitamins, the sex hormones, the cardiac glucosides, and some of the active substances of the adrenal cortex. The book will be of value largely to the chemical worker in the sterol field. Chapters upon the history of the subject, specialized methods of research, and upon the chemistry of bile acids are given as an introduction to the compendium upon physical constants. A complete bibliography is furnished at the end of the work, as well as a separate, convenient appendix of simplified structural formulas for 404 different sterol derivatives.

D. D.

SURGICAL PATHOLOGY. By WILLIAM BOYD, M.D., LL.D., M.R.C.P. (Ed.), F.R.C.P. (Lond.), Dipl. Psych., F.R.S.C., Professor of Pathology, University of Toronto. Pp. 886; 476 illustrations and 15 colored plates. Fourth Edition, thoroughly revised. Philadelphia: W. B. Saunders Company, 1938. Price, \$10.00.

IN this edition, which appears after an interim of 5 years, an introductory chapter which had been omitted from the third edition has been reinserted by request. "Among subjects which have been added to the present edition are the following: lymphogranuloma inguinale, primary thrombosis of the axillary vein, the grading of malignant tumors, glomus tumor (glomangioma) pilonidal cyst, uveo-parotid tuberculosis, Hashimoto's disease, parathyroid tumor, tuberculosis of the stomach, autolytic peritonitis, regional ileitis, ureterocele, the group of ovarian tumors comprising granulosa cell tumor, Brenner tumor and arrhenoblastoma, the pathology of the intervertebral disks, Gradenigo's syndrome, Clutton's joints, turban tumor of the scalp, and tumors of the islets of Langerhans. . . . New material has been included in relation to the experimental production of cancer, the etiology of tumors, heparin and thrombosis, mesenteric thrombosis, liposarcoma, implantation dermoids, carcinoma of the tongue, the relation of the hypothalamus to gastric ulcer, acute intestinal obstruction, the etiology of appendicitis, carbuncle of the kidney, the pathogenesis of renal calculi, endometrial hyperplasia, anaërobic streptococci in puerperal sepsis, the relation of chronic mastitis to carcinoma of the breast, and Ewing's tumor of bone." (Preface.)

E. K.

REFRACTION OF THE EYE. By ALFRED COWAN, M.D., Associate Professor of Ophthalmology, Graduate School of Medicine, University of Pennsylvania; Attending Ophthalmologist, Philadelphia General Hospital, etc. Pp. 319; 172 illustrations and 3 colored plates. Philadelphia: Lea & Febiger, 1938. Price, \$4.75.

THIS book on the refraction of the eye is unique in approaching the subject from the point of view of physiological optics. Most textbooks

on optics give no consideration to practical refraction, and the majority of ophthalmologists who write on practical refraction are not sufficiently conversant with geometric optics to deal with this most important fundamental basis of their subject.

Dr. Cowan has been teaching optics in the Graduate School of Medicine of the University of Pennsylvania for 19 years, and is widely known for his ability in correlating the theoretical and practical aspects of his subject. He has written a text which is badly needed and which will be found of value to all who are interested in the prescribing of glasses. F. A.

THE HISTORY OF BACTERIOLOGY. (University of London Heath Clark Lectures, 1936, delivered at The London School of Hygiene and Tropical Medicine). By WILLIAM BULLOCH, M.D., F. R. S., Emeritus Professor of Bacteriology in the University of London. Pp. 422; illustrated. New York: Oxford University Press, 1938. Price, \$3.75.

THE bibliographical references to Bacteriology in the appendix of Garrison's History include only one independent work, Loeffler's *Vorlesungen* (1887), which was never completed. In 1930, Bulloch wrote an opening historical chapter in the Medical Research Council's *System of Bacteriology* which has stood for several years as the most satisfactory presentation of the subject. Having to give the Heath Clark lecture in 1936, Bulloch has now expanded his chapter of 103 pages into the present work. A large bibliography and alphabetically arranged biographical notices have been added and various sections expanded. The 11 chapter headings remained substantially as in the earlier effort. Carefully prepared by an authority on the subject, this book is valuable and reliable, though not perhaps as easy reading as the popular historical volumes now in vogue that seem not to hesitate to mix fact and fancy. E. K.

LIFE, HEAT AND ALTITUDE. Physiological Effects of Hot Climates and Great Heights. By DAVID BRUCE DILL, Fatigue Laboratory, Harvard University. Pp. 211; 25 illustrations. Cambridge: Harvard University Press, 1938. Price, \$2.50.

THIS is a delightfully written essay, suitable both for the intelligent layman as well as for the physician and physiologist. Chemical and physiological data, secured from subjects exposed to the need for adjustment to the different conditions of life upon "the hot, low-lying deserts of the southwestern United States and the high, cold prairie or *puna* of South America" form the main topic of the work. Although it may appear to some that extreme adjustments to environmental conditions need be rarely necessary for the average organism, still the borderlands of physiology are extended by such studies. Practical value is also evident in such applications as aviation, mining, etc.

It is the opinion of the reviewer that the work is truly worthy of inclusion in the active library of all who are curious as to the possibilities and limitations of the human organism, under conditions of stress. D. D.

LIFE AND LETTERS OF FIELDING H. GARRISON. By SOLOMON R. KAGAN, M.D. With an Introduction by Professor JAMES J. WALSH. Pp. 287; 3 illustrations. Boston: The Medico-Historical Press, 1938. Price, \$3.00.

WRITER of the world's most successful one-volume History of Medicine, eminent medical bibliographer and librarian, possessor of an arresting, vivid personality, Garrison well deserved, even was bound, to have his Life and Letters published. Yet one is surprised to find so soon a volume, which from the date on the Preface, appears to have been completed within 5 months of his death in April, 1935, though not published until 1938.

It contains notable material. The 7 chapters of Part I (77 pages) deal with his life and accomplishments under such headings as: "General Survey of Garrison's Life;" "Medical Historian and Medical Bibliographer;" "Medical Biography;" "The Teacher;" "Love of Music;" "The Man;" "Tributes." Wisely, most of the book is filled with his own letters, versatile, interesting, frequently pungent and intentionally provocative, and most revealing of the man. A bibliography and 4 appendices conclude the volume. Though containing a considerable number of typographical errors, the book has value. Its appearance sharpens anticipation of the volume that we understand is being prepared by Sigerist. E. K.

INJECTION TREATMENT OF VARICOSE VEINS AND HEMORRHOIDS. By H. O. MCPHEETERS, M.D., F.A.C.S., Formerly Director of Varicose Vein and Ulcer Clinic, Minneapolis General Hospital; Attending Physician, New Asbury, Fairview and Northwestern Hospitals, Minneapolis, and JAMES KERR ANDERSON, M.D., F.A.C.S., Instructor in Surgery, University of Minnesota School of Medicine; Fellow, American Proctologic Society, etc. Pp. 315; 82 illustrations. Philadelphia: F. A. Davis Company, 1938. Price, \$4.50.

MCPHEETERS has rewritten his former book on the injection treatment of varicose veins and has been joined by Anderson, who has contributed a section on the injection treatment of hemorrhoids. The section on varicose veins written by McPheeters has been liberally revised, with enlarged chapters on anatomy and especially on embryology of the veins of the lower extremities. He has given good description of the involvement of the valves in the veins of the extremities. In the chapter on diagnosis he has gone into detail to point out the differential signs. The chapters on the Trendelenburg test and the pathology associated with varicose veins are similar to those in his previous book. One chapter is devoted to the question of operation in varicose veins. McPheeters, however, is more inclined to treat enlarged veins by injections. He believes that failure of injection treatment is due to imperfect technique. Ulcers of veins are treated by the author by the use of sponge pressure at the ulcer site and with the patient ambulatory. In large ulcers, after the tissues have become more healthy in appearance, he advises excision of the ulcer and applies skin grafts.

In the section on the injection treatment of hemorrhoids the usual outline is followed. The author recommends that hemorrhoids to be successfully injected must be internal, and should not protrude, or if at all only with defecation. Constant prolapsing of hemorrhoids is a contraindication to injection. He believes that only 25% of the internal hemorrhoids can be cured by injection alone, another 50% can be cured by injection and surgery. Those in which surgery is necessary are cases having an external varicosity which cannot be cured by injection. He believes that large prolapsing, fibrosed hemorrhoids or those associated with other anal lesions should be treated by operation. He describes the technique of injection and gives the various types of solutions which may be used. One is led to believe that the author feels the injection treatment of hemorrhoids is one not too sure of permanent result and not too free from complications.

L. F.

TRIUMPH OVER PAIN. By RENÉ FULÖP-MILLER. Translated by EDEN and CEDAR PAUL. Pp. 438; illustrated. Indianapolis: The Bobbs-Merrill Company, 1938. Price, \$3.50.

We cannot but regret the time spent in scanning this book. Instead of a well proportioned "story of mankind's age-old struggle with the problem of physical suffering, from beyond the dawn of history to that astonishing day when a little Boston dentist made the use of ether practical," we find a brief and unsatisfactory preliminary account of the battle with pain—

which up to the 19th century occupies 26 pages—while the overworked “ether controversy” occupies more than half the book (230 pages). Even this is not presented with historical accuracy. Whether in accordance with the Prefatory Note, “using his imagination the dramaturge conjures up the scene” recklessly, or whether from a desire to exalt Morton, at any rate the author fails to give Crawford Long the credit that history has definitely awarded him. It is *not* true that Long lacked confidence in his method, that he gave up the use of ether or that the news of his discovery did not spread beyond the confines of Jefferson. It is true that circumstances, certainly not discreditable to Long, prevented promulgation of his discovery; just as the statement on the Boston monument of the Good Samaritan is also true that ether anesthesia was “first proved to the world” by Morton in 1846.

The emotional, unreliable tone of the book is set in the Prefatory Note: “My book is the outcome of personal experience of pain, and is an attempt of the reason to unravel its mystery. . . . To liberate mankind from pain, heaven and hell were opened. . . . In virtue of his creative privilege, he (the dramaturge) breathes into the dead past until it regains a living soul.” One would prefer a little less vivid drama, and a little more sober history, such as to include an account of the soporifics used so successfully in the Middle Ages, and a reasonable portrayal of the tremendous advances in anesthesia since Simpson’s use of chloroform. But perhaps the versatile author, “who has written a number of books, including the popular ‘Rasputin, the Holy Devil,’ ” was concerned with writing a good seller, and perhaps he was not overburdened with knowledge of his subject.

E. K.

SULFANILAMIDE THERAPY OF BACTERIAL INFECTIONS. With Special Reference to Diseases Caused by Hemolytic Streptococci, Pneumonococci, Meningococci and Gonococci. By RALPH R. MELLON, M.D., DR. P.H., D.Sc. (Hon.), Director, Institute of Pathology, The Western Pennsylvania Hospital, Pittsburgh; PAUL GROSS, M.D., Pathologist to the Institute, and FRANK B. COOPER, M.S., Research Chemist to the Institute. Pp. 398; 16 illustrations and 28 tables. Springfield, Ill.: Charles C Thomas, 1938. Price, \$4.00.

THE Authors’ careful review of the literature and summary of the present knowledge of Sulfanilamide therapy should be extremely valuable to those unacquainted with the subject. The first section deals with the Chemistry and Pharmacology of the Sulfanilamide compounds together with their experimental and clinical employment; 200 different compounds are listed in the order of their relative activities. The second section reviews the experimental work done by the authors with particular emphasis on experimental pneumococcal infection. The third section is devoted to a study of the mechanism of action of sulfanilamide and the mobilization of the defensive factors in the host. The mode of action of these compounds continues to be a stumbling block. This presentation is especially good and although it does not completely clarify the issue, it seems to go a long way in the right direction. The experimental work dealing with the part played by the defensive factors of the host is most stimulating. The fourth section is devoted to general chemotherapeutic considerations with a discussion of the difficulty of evaluating therapeutic efficiency. The book closes with an addenda of work that has appeared after the manuscript had gone to press.

This book will be a valuable reference to the early work on Sulfanilamide therapy. As such its value stops there, as the volume of literature continues to increase from day to day. Already a dozen or more articles have appeared on the use of a new compound since publication that would appear to be better than any of the 200 listed. In the preface the authors seemed unduly

anxious to claim with two other workers in Baltimore the priority of introduction of the new drugs to this country. Cases, however, were treated in New York several months before any in Pittsburgh, and in Philadelphia at the same time as in Baltimore.

D. P.

PATHOLOGICAL TECHNIQUE. A Practical Manual for Workers in Pathological Histology Including Directions for the Performance of Autopsies and for Microphotography. By FRANK BURR MALLORY, A.M., M.D., S.D., Consulting Pathologist to the Boston City Hospital, Boston, Mass. Pp. 434; 14 illustrations. Philadelphia: W. B. Saunders Company, 1938. Price, \$4.50.

MANY years have elapsed since the appearance of the last edition of Mallory and Wright's Pathological Technique, and also since the death of the junior author. During that time technical methods have changed considerably and many valuable new ones have been added. "Clinical Laboratory Methods" and "Bacteriological Methods," subjects included in the older book, have also greatly changed and expanded, and a number of excellent books on these subjects are now available. It was undoubtedly, then, a wise step to omit them from the present work, which, though having the same title as the other volume, is put out as a first edition and in a changed format. Somewhat longer than the postmortem and histologic portions of the older book, and with a different order for the main subjects, the text is frequently reminiscent of the other work and old friends often appear among the illustrations. This is probably to be attributed more to the excellence of the earlier text than to failure to include modern improvements. Descriptions of older methods often remain quite unchanged, as indeed might well be the case from the reader's point of view. However, a gratifying number of new methods have been included, fulfilling the author's wish to present "a selection of those formulas that practical experience has shown to be of value," rather than "an encyclopedia of methods presented historically." The bracketted dates of announcement of many of the methods is a welcome addition, that one would have liked to have seen employed throughout. "Autopsy Methods," which now follows "Histological Methods" as Part III, has been made more useful by the addition of a section on autopsy permissions and inclusion of variants to the Virchow technique. A chapter on gross and microscopic photography is a good addition, though we regret that color photography was not also included. To older pathologists and technicians this volume will be welcome as a successful example of rejuvenation; for the younger generation it should soon make for itself a valued association.

E. K.

THE FOOT. By NORMAN C. LAKE, M.D., M.S., D.Sc. (LOND.), F.R.C.S. (ENG.), Senior Surgeon and Lecturer on Surgery, Charing Cross Hospital; Surgeon, Bolingbroke Hospital, etc. Pp. 366; 353 illustrations. Second Edition. Baltimore: William Wood & Co., 1938. Price, \$4.50.

THE second edition has improved its anatomical plates with colored illustrations. It has added two additional chapters. The one on "Congenital Club Foot" omits from its treatment the most effective conservative measures for resistant or recurrent deformity and advocates surgical procedures which should have been abandoned. The other chapter on "Foot Problems" should have included "traumatic osteoporosis," which again failed to be mentioned in the book. The chapter on "Flat Foot" has remained obscure in its presentation of treatment by manipulations, strap-pings, supports and exercises. This second edition detracts nothing from the value of the first.

J. N.

ELECTROTHERAPY AND LIGHT THERAPY. By DR. RICHARD KOVÁCS, M.D., Clinical Professor and Director of Physical Therapy, New York Polyclinic Medical School and Hospital; Physician in Charge Physical Therapy, City Hospital, New York, etc. Pp. 744; 307 illustrations and 1 colored plate. Third Edition. Philadelphia: Lea & Febiger, 1938. Price, \$7.50.

THIS book is the third edition in the short period of 5 years. The previous editions have been accepted as standard reference books on the subject of Physical Therapy; the appearance of this one shows the demand for such a work. In a rapidly growing subject, such as this, there are many changes in a period of 5 years. In this volume Dr. Kovács has brought Physical Therapy up to date with particular attention to the newer developments.

Short wave diathermy which has been of paramount interest in the past few years is thoroughly covered and a rational method of employing it has been elaborated. So many new machines are offered the physician that a clear exposition of short wave diathermy will be welcomed by the average physician.

The rest of the book describes various forms of treatment in which Physical Therapy is of value, laying stress on the physiologic effects. It enables the student to get a good general idea of the application of Physical Therapy as a whole.

This book is well arranged, covers the subject thoroughly, and in an up to date manner. A glossary of terms and a complete index increase its usefulness. It is well illustrated and should be in the hands of everyone interested in the subject of Physical Therapy. A reliable textbook in Physical Therapy has been badly needed and this book will be a valuable addition for the use of the student and the practitioner as well.

W. S.

LEHRBUCH DER PHARMAKOLOGIE, TOXIKOLOGIE UND ARZNEIVERORDNUNG. By DR. MED. EMIL STARKENSTEIN, O. ö. Professor of Pharmacology and Pharmacognosy in the German University in Prague. Pp. 758; 40 illustrations. Vienna: Franz Deuticke, 1938. Price, Paper, M. 20; Bound, M. 23.

THIS book is an attempt, by one of the senior pharmacologists of Europe, to emulate the well-known text of Meyer and Gottlieb in presenting the scientific basis of drug therapy by discussing the effects of drugs upon the various physiological systems of the body. As in its predecessor, a brief summary of the normal physiology opens each of these discussions, but here an attempt is made also to present some of the abnormal physiology involved in drug actions. Although the scope and plan of the book are extremely attractive, the Reviewer cautions the American reader that many of the statements concerning physiology and pharmacology are very different from those current in this country, and since there is no bibliography, and since authority for these statements usually is not indicated, the average reader will be unable to decide whether he is reading about authentic advances in knowledge or about opinions more or less peculiar to the author. Thus, while it may be true—as the author states—that strychnine and atropine do not stimulate anything directly but only remove inhibitions, that viewpoint is scarcely justified by existing evidence. Nor is it apparent to the Reviewer why the author should state categorically that tolerance to morphine probably depends largely upon deranged function of the suprarenal cortex. His opinion that methylene blue is useful in the treatment of carbon monoxide poisoning is no longer widely held in this country, and American readers will wonder at his statement that chewing tobacco con-

tains no nicotine. No mention is made of cyclopropane, nor of the use of barbiturates and ephedrine to reduce the hazards of local and spinal anesthesia, though these developments originated in this country a number of years ago. On the other hand, the sections on vitamins and hormones are well done and up to date. On the whole, the book may have limited value for the specialist in pharmacology but it certainly cannot be recommended to the American student and physician for the purpose for which it was intended; namely, to give the student or physician a comprehensive and trustworthy basis for bedside therapy. C. S.

NEW BOOKS.

The Medical Clinics of North America, Vol. 22, No. 5 (New York Number, September, 1938). Pp. 320; 45 illustrations. Philadelphia: W. B. Saunders Company, 1938.

Endocrine Therapy in General Practice. By ELMER L. SEVRINGHAUS, M.D., F.A.C.P.; Professor of Medicine, University of Wisconsin, Madison, etc. Pp. 192; 39 illustrations. Chicago: The Year Book Publishers, Inc., 1938. Price, \$2.75.

Behandlung Rheumatischer Erkrankungen mit Ultra-Kurzwellen. By PROF. DR. ERWIN SCHLIEPHAKE, Leitendem Arzt der Balserischen Stift. Band 8 of *Der Rheumatismus, Sammlung von Einzeldarstellungen aus dem Gesamtgebiet der Rheumaerkrankungen*. Herausgegeben von PROFESSOR DR. RUDOLF JÜRGENS, Berlin. Pp. 105; 27 illustrations. Leipzig: Theodor Steinkopff, 1938. Price, Rm. 7.00.

Drastische Hautreizbehandlung. Heilwege bei Inneren Erkrankungen. By DR. WALTER RUHMANN, Spezialarzt für Innere Krankheiten in Berlin. Pp. 115; 20 illustrations. Leipzig: Krüger & Co., 1938. Price, Paper, M. 3.80; Bound, M. 4.80.

Der Zyklus der Frau. Reform des Ehelebens. By DR. JULES SAMUELS, Chirurg-Frauenarzt, Leiter der Einrichtung für Kurzwellentherapie, Amsterdam. Pp. 175; 43 illustrations (some in colors). Hague: G. Naeff, 1938. Price not given.

Dental Science and Dental Art. Edited by SAMUEL M. GORDON, PH.D., National Research Council Fellow (Biological Sciences) 1926-1928; Director, American Dental Association Bureau of Chemistry, and Secretary of the Council on Dental Therapeutics, American Dental Association, 1928-1937. Nineteen Contributors. Pp. 731; 224 illustrations and 61 tables. Philadelphia: Lea & Febiger, 1938. Price, \$9.50.

Modern Anaesthetic Practice. (The Practitioner Handbooks.) Edited by SIR HUMPHRY ROLLESTON, BT., G.C.V.O., K.C.B., M.D., F.R.C.P., and ALAN A. MONCRIEFF, M.D., F.R.C.P. Pp. 231; illustrated. London: Eyre & Spottiswoode (Publishers), Ltd., 1938. Price, 10s. 6d.

Insulin. Its Chemistry and Physiology. By HANS F. JENSEN, PH.D., Associate, Laboratory for Endocrine Research, The Johns Hopkins University. Pp. 252. New York: The Commonwealth Fund, 1938, Price, \$2.00.

Bulletin of the Health Organisation of the League of Nations, Vol. 7, Nos. 1, 2 and 3. (February, April and June, 1938.) Pp., No. 1, 1-167; No. 2, 168-427; No. 3, 427-607; all illustrated. New York: Columbia University Press, 1938. Price, 65c each; annual subscription (6 numbers), \$3.75.

Jacob Henle: On Miasmata and Contagia. Translated by GEORGE ROSEN, M.D. Pp. 77; 1 illustration. Baltimore: The Johns Hopkins Press, 1938. Price, \$1.00.

Biology and Pathology of the Tooth and Its Supporting Mechanism. By BERNHARD GOTTLIEB, Research Professor, Columbia University Dental School, etc., and BALINT ORBAN, Assistant Professor, Northwestern University Dental School, Chicago, etc. Translated and Edited by MOSES DIAMOND, Associate Professor, Columbia University Dental School, New York; Head of Dental Anatomy Department. Pp. 195; 166 illustrations. New York: The Macmillan Company, 1938. Price, \$5.00.

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NEW EDITIONS.

Human Pathology. A Textbook. By HOWARD G. KARSNER, M.D., Professor of Pathology, Western Reserve University, Cleveland, Ohio. With an Introduction by SIMON FLEXNER, M.D. Pp. 1013; 461 illustrations (18 in color). Fifth Edition, revised. Philadelphia: J. B. Lippincott Company, 1938. Price, \$10.00.

The Practice of Medicine. By JONATHAN CAMPBELL MEAKINS, M.D., LL.D., Professor of Medicine and Director of the Department of Medicine, McGill University; Physician-in-Chief, Royal Victoria Hospital, Montreal, etc. Pp. 1413; 521 illustrations (43 in color). Second edition. St. Louis: The C. V. Mosby Company, 1938. Price, \$12.30.

Appendicitis, omitted from the first edition as a surgical condition, has been included in this edition. "Among the conditions which have been amplified or added are the following: acute laryngotracheobronchitis; tuberculous tracheitis; 'cysts' of the lung; Friedländer pneumonia; lipoid pneumonia; monocytic leucemia; nutritional edema; protamine zinc insulin; experimental nephritis; vascular renal failure; congenital aplasia of the kidney; uremic state; sulphanilamide therapy; lymphogranulomatosis inguinalis; epidemic pleurodynia, and cannabis indica intoxication." The numerous illustrations—an unusual and valuable feature of a textbook on the Practice of Medicine—have been revised and amplified. E.K.

Interns Handbook. A Guide, Especially in Emergencies, for the Intern and the Physician in General Practice. By Members of the Faculty of the College of Medicine, Syracuse University. Under the Direction of M. S. DOOLEY, A.B., M.D., Chairman, Publication Committee. Pp. 523. Second Edition, revised and reset. Philadelphia: J. B. Lippincott Company, 1938. Price, \$3.00.

Intern and practitioner will here find a wealth of practical information, much of it of a type useful in emergencies and gathered by many collaborators not only from textbooks but also from medical journals, all of it encompassed in a handy little pocket-size volume. It is highly recommended. R.K.

The Principles and Practice of Perimetry. By LUTHER C. PETER, A.M., M.D., Sc.D., LL.D., F.A.C.S., Professor of Ophthalmology in the Graduate School of Medicine of the University of Pennsylvania; Ophthalmologist to the Graduate Hospital of the University of Pennsylvania, etc. Pp. 331; 222 illustrations and 5 colored plates. Fourth Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, \$4.50.

PROGRESS OF MEDICAL SCIENCE

OTO-RHINO-LARYNGOLOGY.

UNDER THE CHARGE OF

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RECENT ADVANCES IN PLASTIC AND RECONSTRUCTIVE SURGERY OF THE EAR, NOSE AND THROAT.

THE demands for reparative and reconstructive procedures about the head and neck are becoming more frequent. This is due in no small measure to the increasingly large number of deformities subsequent to industrial hazards and automobile accidents. A further factor is the slow but definite change in attitude towards plastic surgery from the earlier view that it was only the sphere of the plastic quack or pseudosurgeon. It is acknowledged today that there is a definite indication for these procedures, not only from the esthetic point of view but also as a means of economic rehabilitation, as well as a measure to prevent or treat the ever-present phobia or psychoneurosis. It is highly suggestive of the trend of the times to note that departments of plastic surgery are being brought into existence in hospital after hospital. This tendency is in support of the contention of Davis^{16a} that a special branch of surgery has come into existence. In this same contribution he outlines the type of organization that he considers should be adopted by large institutions in order that such service may be available in every community. The possibilities of scientific and honest plastic surgery providing it is practiced by skillful, honorable and qualified surgeons is discussed by Beck,⁶ who comments on the aims and future of this specialty and traces its development. The medico-legal aspects of plastic surgery, which may be of much practical importance, has received scant attention in the literature. Maliniac^{37a} contributes a lengthy and minute exposition of the subject. He decries the indolence of the legal and medical profession in protecting the public against the unqualified and quack practitioners, and believes that greater aid should be extended to qualified and well-trained surgeons who employ recognized methods in relieving functional and anatomic abnormality. He feels that the possibilities of expert repair

should be taken into account in consideration of the amount of indemnity for deformities arising from industrial and other causes. More information along these lines should be available to hospital staffs and executives that are hesitant in recognizing or creating such departments. The recent announcement of the formation of the American Board of Plastic Surgery is further confirmation of the definite existence of this specialty. The functioning of this examining board will assure the public of properly qualified surgeons. Plastic surgery is an intimate part of ophthalmology, otolaryngology, maxillofacial and oral, and dental, as well as general surgery. Blair^{5a} believes that the basic training should be a thorough grounding in general surgery. Hays²⁸ advocates that the otolaryngologist perform the plastic procedures in the repair of tracheotomy wounds, pharyngeal adhesions, septal perforations, auditory canal atresias, postauricular fistulæ and outstanding ears.

In consideration of indications for plastic and reconstructive procedures, gross deformity or abnormality has been accepted by the profession with little if any question. On the other hand, minor defects and slight deviations from the normal, as a rule, have been denied correction by orthodox practitioners in the past. The mental anguish that many individuals with but slight defects experience, not infrequently may lead to a definite psychoneurosis or real psychosis. Blair^{5b} discusses in a masterful way the psychic reactions and the attendant handicaps of such individuals. In a group of illustrative cases of various types of facial defects associated with various manifestations of mental trauma, he definitely assumes the attitude that the indications for surgical repair require a consideration of the psychic reaction as well as the featural deformity. Gillies and Mowlem²³ also insist that early treatment of physical defects definitely reduce the incidence of secondary psychologic trauma to a minimum. Straith,^{59a} in an extensive dissertation on the psychologic aspects of plastic surgery, discusses at great length the psychic distress and feeling of inferiority, that many individuals exhibit with featural defects. Using a large series of cases he describes the success that has attended such procedures in socially, mentally and economically rehabilitating these unfortunates. It is generally conceded that an abnormality that is sufficient to impair function or interfere with social intercourse or economic endeavor, not only is admissible but is actually desirable of repair. However, we have had difficulty when presented with a slight disfigurement that is not objectively conspicuous. It is admitted that all individuals vary in their mental reactions. We have repeatedly observed patients with monstrous defects that are actually repellent to the observer in whom little if any psychologic disturbance is evident. On the other hand, we have more frequently observed an unusual psychic disturbance markedly out of proportion to a minor or infinitesimal defect. Our experience with such individuals is a most unhappy one. More often than not, the procedure has not influenced the mental condition unless, to exaggerate it. Maliniac^{37b} has had similar experiences, and advises a careful psychologic appraisal of the patient with a defect out of all proportion to the mental state that is exhibited. Such psychic instability should be an absolute contraindication for the procedure, as the surgery may supply a new focus for the obsession.

Not infrequently such an obsession may appear after the operation and the subsequent course may be trying to the surgeon and patient alike, who exhibited no such mental abnormality before operation. In consequence, we are reluctant to accept individuals with but minor defects unless there is a good motive underlying the request. It might be well when in doubt to seek psychiatric consultation and avoid subsequent regret.

Nasal Plastics. Plastic surgery of the nose is, in all probability, the most common procedure within this field that the otolaryngologist is called upon to perform. The operations for removal of an unsightly hump or the correction of a depressed dorsum have been fairly well standardized. In the case of the depressed dorsum or saddle nose, the usual procedure is to effect a subcutaneous elevation of the soft tissues above the bony dorsum and insert some rigid material for support. In addition to bone and cartilage, foreign bodies such as celluloid and ivory have been utilized. Notwithstanding the known temporary tolerance that tissues have for foreign bodies, reports of their continued use appear. Mortnick⁴⁰ advocates the use of ivory, and Golden²⁴ advocates the use of celluloid as well. Maliniac, who originally introduced the use of ivory into this country, no longer employs the material. In our own hands, the number of expulsions were so great that we discontinued their use some 10 years ago. A real innovation is the use of preserved isografts of cartilage, that is reported by Spanier⁵⁸ and by Straith and De Kleine.⁶⁰ Cartilage obtained from another person is preserved in an aqueous solution of merthiolate and kept in a refrigerator. They report that the percentage of takes with this material compares favorably with fresh autogenous cartilage removed from the patient. This may be the answer to the situation when an individual refuses to supply a supporting substance from some other part of his body. Cartilage continues to give better end results than bone. We have noted that bone has a tendency to atrophy and become absorbed, in spite of repeated assertions that bone implants will live if placed in contact with bone. McIndoe,^{34a} in treating on the restoration of nasal depressions with cartilage grafts, notes that although cartilage will live when placed within living tissue, bone may disintegrate and he calls attention to the fact that the use of bone only is attempted by those that do not keep pace with the literature. He gives the results of experiments with cartilage grafts in various forms utilized in depressions of different degrees. Depressions and deformities of the nasal tip are treated in great detail by Straith.^{59b} The nature and extent of the deformity determine the procedure he employs. Small defects in the skin are covered by Wolfe grafts obtained from the upper eyelid or back of the ear. Defects of the ala are corrected by small flaps from the nose or nasolabial folds. Extensive losses of tissue require delayed flaps from other parts. Slight cartilaginous depressions just above the tip are repaired by the introduction, subcutaneously, of small pieces of auricular cartilage. Broad depressions necessitate the use of rib cartilage or Straith's modification of Kazanjian's procedure, in which he everts the cut ends of the upper lateral cartilages and sutures them back to back in the midline to provide support. A simple method of reducing an abnormally protruding nasal tip is described by Wahl.⁶³

A method of correcting a lateral deviation of the nasal tip by means of excision of the large asymmetric triangular cartilage is described by Tamarin.⁶¹ A most detailed and complete presentation of the repair of nasal deformity due to loss of tissues from various causes is presented by Pierce and O'Connor.⁵⁰ In this article they stress the use of pedicled grafts obtained from neighboring parts.

Plastic procedures about the nasal tip are not restricted to anatomic deformities. Not infrequently impaired nasal respiration may be due to a congenital weakness of the nasal ala causing them to be drawn in during inspiration. Upon elevating the tip of the nose, so as to prevent the tissues from being inspired, the obstruction to breathing may be eliminated. Rethi⁵² describes a method of stiffening the ala, by removing a piece of the lateral crus of the alar cartilage, so as to effect a non-yielding scar, or by excising a sickle-shaped piece of skin that raises the alar cartilage away from the septum. Organic stenosis of the anterior nares is treated by O'Connor^{44a} by excising the stenotic tissues and replacing them by a Thiersch graft. Nasal obstruction due to a lateral displacement of the lower part of the septum into one nostril or the other may be a cause of poor respiration as well as disfigurement. Operative procedures for repair of this condition are described by Metzenbaum,³⁹ Cohen,¹³ and Peer.⁴⁸ Congenital bony atresia of the posterior nares with operative cure is described by Kearney,³² Colver,¹⁴ Anderson,¹ Donnelly,¹⁸ and Childrey.¹² The tendency for the opening to undergo cicatricial stenosis was overcome by Donnelly¹⁸ in the use of a whole skin graft.

The management of nasal fractures constitutes one of the most important phases of rhinoplasty. As far as our personal experience is concerned, the primary treatment of such fractures apparently receives but cursory attention at the hands of the profession. While some attempt is made towards repositing the fragments to secure as little external deformity as possible, most individuals make little if any effort to investigate the internal architecture of the fractured nose to determine whether or not a patent airway is present and maintained. The increasing number of nasal and facial fractures as a result of the automobile, industrial and sport hazard should impress us with the necessity of observing that due precaution is taken in the treatment of these accidents in order to prevent the hazardous sequelæ of nasal deformity and impaired nasal respiration. Most fractures are amenable to reduction and immobilization. As Safian and Tamarin⁵⁵ state, the nose is composed of several individual structures, and unless a detailed analysis of the structures involved is made, the treatment may be incomplete. Straith and De Kleine⁶⁰ insist on careful reposition of the fragments and stabilization by adequate splinting devices. Salinger⁵⁵ advocates the use of soft metal splints, while New⁴² uses a mattress suture passed through the nose and secured with lead buttons in some cases. Watkins^{66a} also emphasizes early replacement and immobilization of the fragments. Watkins^{66b} uses a hairpin-shaped splint. If there is loss of overlying soft tissue Straith^{59b} believes that it should immediately be replaced with a Wolfe graft. Kazanjian,^{31a} in a discussion of nasal injuries, insists that great care must be taken in selection of these grafts from the point of view of texture and coloration as well as visibility. The repair of old unreduced fractures is

treated by McIndoe,^{34b} Fomon,²¹ Straith and De Kleine,⁶⁰ and Safian and Tamerin,⁵⁵ who find that various procedures may be required to repair such uncalled for end results as dislocated septi, dorsal depressions, deviations from the midline, as well as humps and exostoses produced by callous formation. Facial deformity is most commonly due to accidental trauma or disease. At times surgical procedures for carcinoma about the face leave marked postoperative defects. The repair of large defects of the cheek following radical resection for malignantly diseased upper jaws is described by Beck and Guttman,⁷ Prudente,⁵¹ New and Figi,⁴³ and Figi²⁰ by the use of various types of sliding and travelling flaps. A sufficient interval of time should elapse before contemplating the reconstruction in order to assure ones' self that a recurrence of the growth is not likely to be manifested. In the interval, which should be one or more years, an artificial prosthesis may be worn. Olinger and Axt⁴⁵ and Kazanjian^{31c} describe such prosthetic devices in oral and facial defects, and indicate their use when surgical repair is impossible for various reasons. The source of the graft in repairing facial defects is treated by Maliniac,^{37c} who advises a rotating or sliding graft from the immediate area of the defect. Here the color and texture of the skin closely approximates that of the area lost. If this is not feasible then tube grafts from the forehead, back of the ear or from the neck is advised. The early care of face injuries is discussed by Blair, Brown and Byars.¹⁰ They advise immediate suture of all cuts into the ear, border of lip and eyelid, or the nasal skin and underlying cartilage. A most interesting account of the successful healing of a nasal ala that was completely torn away from the nose is reported by Roy.⁵⁴ He sutured the ala to the nose some 3 hours after the accident had occurred. Davis^{16b} describes the use of the vertical mattress suture, and Straith^{60c} describes the use on subcuticular suture in dealing with facial scars.

Nasopharynx. As a result of a poorly performed tonsil and adenoid operation, extensive destruction following a severe Vincent's infection, or infrequently today in comparison with the past, of lues, one may be confronted with a stenosis of the nasopharynx. Pharyngeal reconstruction for such a condition is described by O'Connor,^{44b} who utilizes a Thiersch graft placed into the opening created by the removal of the scarred tissue to prevent its recurrence and subsequent stenosis. There are a number of contributions by Riemke,⁵³ Vaughan,⁶² Blair and Brown,⁹ Ivy,³⁰ Wardill,⁶⁴ and Brown¹¹ on various aspects of cleft palate surgery. A method of utilizing an intratracheal device for anesthesia is described by Ayre³ for use in infants. The mechanism of the soft palate and surrounding structures in the production of speech was studied by Wardill and Whillis⁶⁵ in a patient in whom an operative defect permitted direct vision, while Parsons⁴⁷ reviews the various factors that interfere with the production of normal speech in cases of cleft palate. It was assumed in the past that the characteristic speech, when once developed, persisted after the closure of the palate. However, this type of rhinolalia is due to an inadequate length of the reconstructed palate that does not permit of efficient closure of the nasopharynx. Vaughan⁶² describes a new incision that allows for greater lengthening of the resulting palate that may prevent the occurrence of the speech defect, while Wardill⁶⁴ employs a pharyngo-

plasty to aid in narrowing the nasopharynx. That the repair of the cleft palate is not always accompanied by a successful result at the first attempt is indicated by Padgett,⁴⁶ who reports on 114 cases in which the primary operation was unsuccessful to some degree or other. He describes several procedures in such cases varying with the amount of tissue lost. He finds that these cases had an average of 2.3 % unsuccessful operations per patient.

The abnormally protruding or receding chin also has been subjected to active interference. In the past, operative procedures for increasing the prominence of the chin consisted in the main of the introduction of ivory or preferably costal cartilage subcutaneously. Kazanjian^{31d} and Babcock⁴ describe operations upon the mandible and on displacement of the condyle respectively to aid in accomplishing the same purpose. The mandible is also partially resected and repositioned by Kazanjian,^{31d} Hensel,²⁹ and Pettit⁴⁹ in reconstructing the protruding jaw of prognathism.

The closure of laryngostomic fistulæ and enlargement of the tracheal lumen by means of excision of the cicatrix and the use of a pedicle flap and cartilage is described by Babcock^{4b} and Looper.³³

Plastic surgery of the ear in the past has concerned itself mainly with protruding ears and the closure of postauricular fistulæ. While postauricular fistulæ are relatively uncommon today, a few cases may be seen at rare intervals. The most common cause has been the practice of continuous packing of the mastoid wound until an ingrowth of the dermal epithelium met an outgrowth of the mucosal epithelium of the mastoid antrum. As an aid in the prevention of their occurrence, McNichols³⁵ has described an incision in which the posterior flap is split into two layers that are individually sutured. The same principle is utilized by Ashley² and Copps and McCormick¹⁵ in closing a postauricular fistula, in which he obliterates the mastoid cavity with the inner layer and closes the external defect by the outer layer. Protruding ears can be easily corrected by removing elliptical sections of the auricular cartilage and skin. In the past, the failure to realize a successful result was due to the practice of excising the skin only and suturing the auricle in closer approximation to the head without touching the cartilage. As the elastic auricular cartilage acted as a spring, the constant tension caused the skin to stretch and after a period of time, the ears protruded once more. Davis and Kitlowski¹⁷ report on a new method involving excision of the cartilage that gave excellent results. They feel that the best age for operation is from 4 to 5 years and claim that there is no interference with the subsequent development of the ear. Graham²⁶ and MacCollum³⁶ also describe technique based upon the principle of excision of the cartilage. The surgical attack upon the cartilage brings the possibility of a deforming chondritis into mind. Such a complication can be avoided by strict attention to asepsis and the obliteration of all dead space and crevices in the post-operative dressing. Goodyear²⁵ discusses measures to prevent such a complication. While there has been a great deal of energy expended in attempting to construct an entire ear in cases of congenital absence or rudimentary ears, they have for the most part been absolute failures. Most of the end results were merely the substitution of monstrosity for deformity. However, Gillies²² and Nattinger⁴¹ have reported on

a method of utilizing maternal ear cartilage as a means of support that may offer encouragement in obtaining more pleasing esthetic results. Facial paralysis presents a most arresting deformity. In the past, the use of hypoglossal and spinal accessory nerve anastomosis left a good deal to be desired. Such anastomosis resulted in facial spasms when using the tongue or arm. In addition, facial changes corresponding to emotional changes would only occur on the unaffected side, so that one laughed or showed anger or sorrow with but one side of the face. Sheehan⁵⁷ and Halle²⁷ advocate the use of temporal and masseter muscle slips in association with strips of fascia attached to the angle of the mouth. The most revolutionary tendencies have been in the direction of suture of the facial nerve. A successful direct suture of a divided nerve is reported by Martin³⁸ with the principle of removing the nerve from its bed so as to give the few additional millimeters of length necessary for the approximation of the severed ends. When this is not feasible the procedure of bridging across the defect with a nerve graft from the superficial femoral nerves is described by Ballance and Duel.⁵ The results with this technique so far surpass the use of the method of nerve anastomosis as to relegate the technique into the limbo of medical history. While most cases of Bell's or refrigerant palsy get well, some remain more or less permanent. The condition is due to an edema of the nerve within its non-yielding bony canal with resultant pressure atrophy. Duel and Tickle¹⁹ found that 80% of these cases did not entirely lose their reaction to the faradic current and finally recovered. The remaining 20% lost their faradic response in 2 or 3 days and were permanently paralyzed. The total loss of the faradic response should be the indication for immediate decompression of the nerve in the canal by removal of the overlying bone.

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NEUROLOGY AND PSYCHIATRY.

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ELECTROENCEPHALOGRAPHY.

BERGER⁴ was not the first to demonstrate potential changes arising from the brain, but it was largely his work, coming at a time when advances in the knowledge of electricity had provided suitable apparatus, that stimulated the great mass of research on this phenomenon. That a great deal of work is being done is attested to by the fact that, in the Quarterly Cumulative Index Medicus for the first 6 months of 1938, 37 of the 77 titles listed under Physiology of the Brain deal with some aspect of the electrical activity of the cortex.

Although electroencephalography has been frequently likened to electrocardiography, the analogy is hardly a close one, since the electrocardiogram records action potentials, while at least some of the potentials of the electroencephalogram are ascribable to lack of activity of the units involved. The apparatus is, however, essentially the same,

consisting of electrodes for application over the area to be investigated, an amplifier employing vacuum tubes, and a recording device. Greater amplification is required than with electrocardiography, as the potentials to be recorded are approximately one-tenth as great, varying from 5 to 100 millionths of a volt, when taken by electrodes placed on the scalp. From the exposed cortex, they may be 50 to 100 times this large. The apparatus used by various workers lacks uniformity, both in the frequency characteristics of the amplifiers and of the recording units. When to this is coupled a lack of standard types of electrodes and derivations of the leads, it is not remarkable that some discrepancies between the records obtained by different investigators have resulted.

In general, two types of waves are recognized to occur in the normal subject. The alpha waves, sometimes spoken of as the "Berger rhythm," are characteristically found when the electrodes are placed over the occipital region of a mentally tranquil subject who has his eyes closed. They are of a frequency from 8 to 12 per second, and roughly sinusoidal. They disappear in most subjects on opening the eyes in the light, and in all when reading. Emotional tension also causes them to disappear. They are quite characteristic for form and frequency for each individual,^{27a,b} while in some normal people they do not occur at all. Their rate may be increased up to about 18 per second by exposing the eyes to a flickering light source of similar frequency.¹ It is felt that they are probably representative of the synchronous resting discharge of the neurones of the occipital cortex.³

The beta waves are of lower amplitude and higher frequency, from about 18 to 30 per second. They may be found anywhere over the cortex, but are particularly prominent over the motor area.¹⁰ Some doubt has been cast on their relationship to cerebral activity, and they have so far proven of little importance.

Besides these normal waves, there are waves, to be described later, associated with epileptic seizures, and slow, large amplitude waves of 1 to 6 per second, called delta waves, associated with dysfunction or disintegration of the cortex.

Factors Influencing Normal Rhythms. It has been shown that alpha waves do not appear before the age of about 4 months, and that at this time they are rare, and of a frequency of about 4 per second. This frequency increases with age, until at 8 years they attain the adult average, which is 10.2 per second in men and 11.0 in women.²³ This correlates well with the findings in mental defectives, where the alpha rhythm is slower than normal for mental ages below 5 years, and normal above that mental age.²⁰

The state of consciousness has a marked effect on the alpha rhythm. Five levels of consciousness associated with falling asleep may be delineated.¹¹ With the subject wide awake, the normal alpha rhythm of 10 per second is present. As drowsiness comes on, the amplitude of the alpha waves diminishes, and they are present less of the time. Then short groups, or "spindles," of waves of 14 per second appear, with occasional low frequency delta waves, which are not present in the normal waking encephalogram. The 14 per second waves then become greater in amplitude, and delta waves become more frequent, until finally in deep sleep there are many large delta waves and spindles of 14 per second waves. Thus it is essential in passing on the normality

of an electroencephalogram to know the state of consciousness of the subject. Hypnosis does not produce the changes characteristic of sleep, but hypnotic suggestion of light will abolish the alpha waves of a subject with eyes shut.^{5,25} Unconsciousness from other causes, as in syncope and in coma from increased intracranial pressure, produces essentially the same changes as does sleep.

Breathing pure oxygen produces no change in the alpha waves,⁸ but asphyxia, as in breathing nitrogen, induces changes characteristic of sleep. Inhalation of 20 % carbon dioxide increases the frequency and decreases the amplitude of the waves, while hyperventilation causes no change until, in the period of apnea, oxygen lack calls forth the same changes as are seen in asphyxia.

A significant relationship has been shown between basal metabolic rate and alpha rhythm, the latter being increased in rate in subjects with a high metabolic rate, whether due to thyroid disease or induced by thyroxin injection. No significant relationship with pulse, blood pressure, or body temperature could be demonstrated.²⁴ The shift in rate during the advancing progress of cortical involvement in paresis probably reflects shifts in the cellular respiration rate of the cortical cells.¹⁷

Those drugs which alter the state of consciousness are particularly effective in changing the alpha rhythm. Bremer^{7a} has shown that ether and chloroform produce a slowing of the rhythm, which he believes is due to a marked depressant action on the cortical cells. Barbiturates, on the other hand, increase the amplitude of the already present alpha rhythm, an effect similar to that seen in animal preparations in which the cortex is separated from its lower centers surgically.^{7b} He believes that this is due in both cases to an effective de-afferentation of the cortex, allowing the cells to beat synchronously at their resting rate, without interference from incoming stimuli.

These results were in part confirmed by Derbyshire *et al.*,¹² who found increased amplitude of alpha waves with light barbiturate anesthesia, but disappearance of waves as the anesthesia deepened. They found waves of 30 to 40 per second in ether anesthesia, sometimes superimposed on large, slow waves. Lennox, Gibbs, and Gibbs²² found barbiturates and bromides to decrease frequency and increase amplitude of waves. The increased amplitude of waves in anesthesia is ascribed by Adrian and Matthews² to the cutting off of afferent impulses which if allowed to reach the cortex would diminish synchronous activity. This is in accord with Bremer's hypothesis.

Mescaline, especially when producing visual hallucinations, tends to suppress the alpha rhythm.²⁶ Small doses of acetylcholine and of potassium by the intracarotid route in animals in which the cortex has been "isolated" increase the frequency of waves, while large doses diminish activity. Calcium in all doses diminishes activity, bearing out the calcium-potassium antagonism.⁶ Strychnine applied locally to the cortex in very dilute solution augments electrical activity, while higher concentrations cause sharp, rapid potentials, due to rhythmic spontaneous discharge of groups of pyramidal cells.^{7c} Alcohol in large doses produces the large, slow waves characteristic of unconsciousness. Scopolamine and morphine first decrease the amplitude of the waves, and later may cause bursts of large waves at a 10 per second rate.

Drugs acting on the autonomic system have not been shown to produce any changes.^{14a}

In Pathologic Conditions of the Nervous System. Lemere^{21b} has shown that in normal individuals the alpha waves are of the same amplitude on the two sides of the head, while in patients with unilateral lesions of the frontal lobe, notably abscess and tumor, the waves on the affected side are of greater amplitude. In lesions of the parieto-temporal regions which destroy the optic radiations, the alpha rhythm remained present on the affected side even with the eyes open, while it disappeared on the unaffected side when the eyes were opened. In widespread lesions destroying the occipital lobe, the alpha rhythm was absent. Jacksonian epilepsy gave rise to large potentials of spike form, while the visual aura of migraine suppressed the alpha rhythm, which later returned while the headache persisted. In organic dementia the alpha rhythm was poorly manifest.

Walter^{29a,b} has demonstrated that abnormally large, slow waves, designated delta waves, are regularly present over areas of cortical dysfunction or disintegration. He has been notably successful in localizing cerebral neoplasms by this means. He utilizes three separate amplifier systems, and by disposing his electrodes over one side of the skull after the manner employed by Adrian, is able to determine the site of origin of the abnormal potentials by observation of their phase relations in the various leads. In 38 cases of suspected tumor, 12 showed delta waves from a single focus, which on operation proved to overlie a tumor. Of the 26 cases showing no abnormality, 23 were ultimately proven to be free from tumor, and of the remaining 3, 2 had cerebellar tumors and 1 an eighth nerve tumor. He called attention to the diffuse presence of delta waves in states of increased intracranial pressure, which must first be reduced before localization is possible. Case⁹ was able to localize a tumor by this means.

Lennox and his co-workers^{13,14b,15} have found abnormal potentials with the occurrence of epileptic attacks. Grand mal attacks are characterized by rapid, spike-like waves, psychomotor attacks by slow waves, and petit mal attacks by a combination of slow round waves and sharp spikes. The characteristic petit mal waves may be seen when the patient is not aware of having an attack. Attacks may be predicted beforehand by the appearance of the characteristic wave pattern, while the effect of therapy may be judged by the action of drugs on the abnormal potentials. Lennox has called epilepsy a "paroxysmal cerebral dysrhythmia," and has stated^{14b} "a clinically observed seizure is but the outward manifestation of a disordered rhythm of brain potentials."

Golla, Graham, and Walter¹⁶ have found pathologic delta waves in about half of some 200 epileptics examined by them. Those patients suffering from grand mal attacks of idiopathic nature almost invariably showed a focus of delta waves on one or both sides of the head. Delta waves were more conspicuous in young than in old epileptics. They found no difference in incidence of delta waves in patients under treatment with barbiturates and bromides and in those not under treatment. On the hypothesis that the presence of delta waves indicated a depression of cortical function, one patient was given a cortical stimulant, benzedrine sulphate, with disappearance of both delta waves and attacks, both of which returned on discontinuing the drug.

Hoagland *et al.*,¹⁸ found that patients with schizophrenia showed an increased incidence of delta waves. He demonstrated that, after a large dose of insulin, the incidence of delta waves bore an inverse relationship to the level of blood sugar, and that some schizophrenics after insulin therapy showed a decrease in the number of delta waves coincidental with clinical improvement.

Travis and Malamud²⁸ found no difference between the electroencephalograms of normal and schizophrenic subjects. They observed that stutterers showed showers of sharp spikes coincidental with their inability to speak. The appearance of these potentials is such, however, as to raise the suspicion that they may be muscle action potentials incidental to the grimacing not uncommon in stutterers under these circumstances.

Schizophrenics have been shown to have a relatively "poor" alpha rhythm, while manic depressives have "good" ones, and this tendency is carried over to non-psychotic individuals of these personality types.^{21a} Hughes, Strecker, and Appel¹⁹ have found waves of a frequency up to 500 per second in schizophrenia, as well as in the apneic phase after overbreathing. These are so far beyond the frequencies previously reported as to make their significance difficult to evaluate.

In mental deficiency, the frequency of the alpha waves seems to parallel mental rather than chronological age, the rate being essentially normal in those mental defectives with a mental age over 5 years.²⁰

Thus it is seen that a great mass of factual data has been secured by the use of the electroencephalograph. The method has been applied to many unrelated pathologic conditions, and it is not surprising that with widely varying apparatus some conflicting results have been obtained. Sweeping conclusions are not justified in the light of the fragmentary data now at hand, yet it is already clear that the electroencephalograph is a valuable tool in the study of nervous function. Whether the potentials recorded are a direct reflection of the activity of the neurones, or are merely a concomitant phenomenon, they give us a tangible evidence of cerebral function which should be of great help in neurophysiology, and is already of clinical importance in the localization of cerebral dysfunction.

HENRY WISE NEWMAN, M.D.

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PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF OCTOBER 17, 1938

Osmotic Pressure Studies on Blood Serum. I. Construction and Calibration of a Thermoelectric Vapor Pressure Apparatus. E. G. WITTING and C. G. GROSSCUP (Abington Memorial Hospital Laboratories, Abington, Pa.). In connection with certain studies on water and electrolytes being carried out in these laboratories it was desired to have a rapid, accurate method of measuring the colligative properties of solutions without employing freezing procedures. Construction of a modified Hill's apparatus is described and preliminary measurements given and discussed.

The apparatus consists of electrically opposed thermal junctions upon which distilled water and the sample solutions are placed. The measurements are made with the thermocouple chambers immersed in a tank of water maintained at a constant temperature by means of a toluene-mercury thermostat. Current output of the thermocouple is read on a high sensitivity Leeds and Northrup galvanometer (sensitivity, 0.0125 microvolts per millimeter under special conditions of operation, coil resistance 16 ohms, external damping resistance 10 ohms).

Electrical circuits are shown and described so that construction could be duplicated if desired.

Osmotic Pressure Studies on Blood Serum. II. Normal and Pathological Human Serum. CHARLES G. GROSSCUP, and JOHN EIMAN, (Abington Memorial Hospital Laboratories, Abington, Pa.). Forty samples of serum from 33 individuals have been analyzed for water, chloride, CO₂ capacity, total protein, urea nitrogen, non-protein nitrogen, glucose, total base, sodium, and equivalent osmotic pressure (EOP). The series includes 6 normals, preëclamptics, standardized diabetics, cases with renal involvement, a hypophyseal cyst and others with chemical imbalance due to various causes.

In each case, except those with elevated non-protein nitrogen, the observed EOP is less than the corresponding total base, despite the presence of significant amounts of glucose and urea in the serum. To account for this apparent discrepancy a careful estimation of the osmotic concentrations of the serum solutes was made for each case. For the

entire series the average ratio observed/calculated EOP is 0.938, with a standard error of the mean of ± 0.005 . Addition of urea and glucose to sera indicated that these substances exerted essentially their calculated osmotic effects. On the assumption that any errors of calculations must reside largely in the electrolyte fraction, an average osmotic coefficient for the salts was computed such that the observed and calculated EOP would agree. This value was found to be 0.86 (Standard error = ± 0.01) in comparison to 0.93 for pure NaCl in water.

A study of the measured acid and base fractions for the 6 normal individuals shows an average total base of 160.3 and an average determined total acid of 159.3. This leaves little room for any substantial error in the base assigned to protein.

Regression equations relating EOP, total base, glucose and non-protein nitrogen are developed. The coefficients of multiple correlations are high, 0.87 to 0.97.

Considering all factors we are inclined to believe that the thermoelectric vapor pressure method, in our hands at least, does not measure the total osmotic pressure of serum but only some (93 to 94%) of it. This fraction is quite constant and suitable correction may be made for it. The method thereby retains its usefulness and has proven satisfactory in the rapid construction of a blood picture for diagnostic and therapeutic measures.

Rhythmic Changes in Blood Flow Through Muscles. LAURENCE IRVING (Edward Martin Biological Laboratory, Swarthmore College, Swarthmore, Pa.). When the Hering-Traube-Mayer type of waves in arterial blood pressure appeared in anesthetized cats, corresponding rhythmic changes were observed in flow through muscle. Flow changes were determined in single muscles by an electrically heated resistance wire indicator operating on the principle of the hot wire anemometer. As blood pressure increased flow diminished in the single muscles. The changes in flow in one muscle were therefore representative of a major part of the peripheral circulation, and the vasoconstriction diminishing flow was the active basis of the change in pressure. Sympathectomy made flow changes in the muscle follow changes in blood pressure passively. The rhythmic changes in circulation were not rapidly altered by vagotomy and cutting the carotid sinus nerves. The rhythm could persist after curarization and artificial ventilation. The rhythmic change in flow, normally controlled over the sympathetic nerves, may be regarded as evidence of the nature of the central mechanism controlling the peripheral circulation. If the rhythmic activity represents a vasomotor center, its operation is quite stable during mechanical alteration of breathing by vagotomy, curarization and artificial ventilation, and frequent periods of apnea produced by inflation of the lungs. The "center" appears to be relatively independent of the control of breathing. Removal of chemoreceptors likewise did not greatly alter the rhythms. This type of peripheral vascular activity, with its possibility of differentiation, should be useful in characterizing the operation of the persistent control of vascular state which is the presumed function of the vasomotor center.

Measurements of the Uterine Contractions in Late Pregnancy With the Lorand Tocograph. D. P. MURPHY (Gynecean Hospital Institute, University of Pennsylvania). Five patients, all pregnant for the first time, were studied with a Lorand tocograph during the last 2 months of pregnancy. Observations were made on an average of 3 times a week. One hundred and six records, which represented approximately 120 hours of observation, gave 1377 uterine contraction waves for study. The wave pattern was similar in the same patient from day to day, but differed widely from patient to patient. There was a steady increase in the measurements of the various uterine motility characteristics as labor was approached, with an unusual increase during the week immediately preceding the onset of labor.

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